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The demography of idiopathic normal pressure hydrocephalus: data on 3000 consecutive, surgically treated patients and a systematic review of the literature

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OBJECTIVE The objective of this study was to describe the demographic characteristics of patients with idiopathic normal pressure hydrocephalus (iNPH) through an analysis of 3000 consecutive, surgically treated Swedish patients and a systematic review of the literature.

METHODS Data on age, sex, comorbidities, diagnostic delay, initial symptoms, and severity of symptoms at diagnosis were extracted from the Swedish Hydrocephalus Quality Registry. In addition, a systematic PRISMA-based review of the literature published from database inception until August 2019 was performed using the PubMed, Cochrane, and Scopus databases on the basis of two concepts: normal pressure hydrocephalus and demography and their association with related terms. Of 1020 unique articles, 16 were eligible for study inclusion and were assessed for quality using the Newcastle-Ottawa Scale. Mean and weighted mean values were calculated.

RESULTS The mean patient age at the time of surgery was 74.4 years, 79% of patients were in their 70s, and 60% of the patients were men. Almost 50% of the patients had symptoms from four main domains (i.e., balance, gait, cognition, and urinary dysfunction) at disease onset. Patients aged < 60 years (2%) reported more headaches and fewer balance problems than those aged ≥ 60. Women were more impaired in function than men at the time of diagnosis. Dementia (Mini-Mental State Examination score < 25) was found in 47% of the patients. Men had more diabetes, heart disease, hypertension, and stroke than women, and comorbidity correlated with increased impairment. The incidence of surgery for iNPH was 20%–40% of the disease incidence according to survey and operation-based studies.

CONCLUSIONS Most iNPH patients undergo surgery in their 70s. Those aged < 60 years show slightly different symptomatology and probably present with a specific disease entity, indicating that the lower age limit for iNPH should be 60 years. iNPH patients have severe impairment preceded by a long diagnostic delay. Even though the included study designs differed, the systematic review showed that the disorder has a very low treatment incidence. The importance of diagnosing and treating iNPH is further emphasized by the fact that iNPH may account for a considerable part of all cases of dementia.

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KEYWORDS idiopathic normal pressure hydrocephalus; demographics; quality registry; systematic review; population based

Idiopathic normal pressure hydrocephalus (iNPH) is a treatable disorder causing gait and balance impairment, cognitive decline, and urinary problems in the elderly.[1,2] Researchers conducting studies of iNPH prevalence have applied different methodologies and have focused on different age intervals; therefore, reported prevalence figures are very divergent, ranging from 1% to 6%.[3,4] Estimated rates of disease incidence and the incidence of shunt operations have indicated that iNPH is largely an underdiagnosed and undertreated disorder.[5–8]

ABBREVIATIONS ASA = American Society of Anesthesiologists; BMI = body mass index; ETV = endoscopic third ventriculostomy; iNPH = idiopathic normal pressure hydrocephalus; miNPH = modified iNPH scale; MMSE = Mini-Mental State Examination; mRS = modified Rankin Scale; SHQR = Swedish Hydrocephalus Quality Registry; WHO = World Health Organization.

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TABLE 1. Ordinal scales for assessment of function in gait, balance, and urinary incontinence (i.e., components of miNPH)*

Score	Gait	Balance	Urinary Continence
1	Normal	Stands independently for ≥30 sec on either lower extremity alone	Normal
2	Slight disturbance of tandem walk & turning	Stands independently for <30 sec on either lower extremity alone	Urgency w/o incontinence
3	Wide-based gait w/ sway, w/o foot corrections	Stands independently for ≥30 sec w/ feet together at heels	Infrequent incontinence w/o the need for a napkin
4	Tendency to fall, w/ foot corrections	Stands independently for <30 sec w/ feet together at heels	Frequent incontinence requiring a napkin
5	Walking w/ cane	Stands independently for ≥30 sec w/ feet apart (1 foot length)	Bladder incontinence
6	Bimanual support needed	Stands independently for <30 sec w/ feet apart	Bladder & bowel incontinence
7	Aided	Unable to stand w/o assistance	Indwelling urinary catheter
8	Wheelchair reliance		

* Components of miNPH based on Hellström et al. *Acta Neurol Scand*. 2012;126(4):229-237.[11]

Descriptions of the demographic characteristics of iNPH patients, such as distributions of age, sex, core symptoms, and comorbidities, are scarce, and no systematic review of the demographics of the disorder exists. Diagnostic guidelines, that is, the Japanese guidelines from 2021[9] and the international guidelines from 2005,[10] diverge on several factors, including age limits, hampering generalizability.

In 2004, the Swedish Hydrocephalus Quality Registry (SHQR) was started to assemble standardized data on the symptoms and signs, surgical procedures, and follow-up of all adults (ages ≥ 18 years) surgically treated for any type of hydrocephalus in Sweden. Demographic data on age, sex, year of symptom onset, initial symptoms, type and severity of symptoms and signs at diagnosis, and risk factors are some of the parameters registered.

Our aim with the present study was to describe the demographic characteristics of the first 3000 consecutive patients surgically treated for iNPH who had been included in the SHQR and to perform a systematic literature review with a focus on the demographic characteristics associated with iNPH.

Methods

Three thousand consecutive patients diagnosed with possible or probable iNPH in accordance with the international guidelines from 2005[10] and treated with shunt surgery or endoscopic third ventriculostomy (ETV; n = 10) were registered in the SHQR from January 1, 2004, to August 8, 2019. All seven neurosurgical university centers in Sweden that perform surgery for hydrocephalus contribute data to the registry: Gothenburg, Linköping, Lund, Stockholm, Umeå, Uppsala, and Örebro. Total national coverage of the surgeries performed by these centers was 80%–95%, depending on the period, as estimated through repeated data validation audits at each center.[8]

Data extracted for this study were as follows: age, sex, diagnostic delay (time in years from the start of initial symptoms to surgery), initial symptoms, presence and type of comorbidity, and scores on scales for the assessment of gait, balance, and continence; on the modified Rankin Scale (mRS);[13] on the Mini-Mental State Examination (MMSE);[12] and on the American Society of Anesthesiologists (ASA) Physical Status Classification System.[15]

Patients' experiences with initial symptoms such as problems with gait, balance, cognition, continence, and headache were dichotomously registered. Gait, balance, and continence utilities were scored using ordinal scales with 8, 7, and 7 levels, respectively, in accordance with the Hellström iNPH scale (Table 1).[11] Each scale score was converted to a minimum-maximum range from 0 to 100, where 0 denotes the most severe deficit and 100 is the performance of an age-matched healthy population. This standardization enabled comparability and reproducibility. A modified iNPH scale (miNPH) score was constructed ([2 × gait + balance + continence scores]/number of included domains [at least 2 required]), allowing for partly missing data.[8] The difference between the miNPH and the original iNPH scale is the omission of the neuropsychological test battery score and the 10-m walking test. These tests were only recently included in the SHQR. The MMSE (score 0–30)[12] and mRS (score 0–5)[13,14] were scored according to established instructions.

Comorbidities of hypertension, diabetes mellitus, heart disease, history of stroke, and intermittent claudication known at the time of diagnosis were registered as present or not. The ASA class[15] was dichotomized into I–II or III–IV. Patients were divided into four age groups: 40 to < 60 years (n = 64), 60 to < 80 years (n = 2369), 80 to < 85 years (n = 466), and ≥ 85 years (n = 101). Incidence of surgery was based on the number of iNPH patients whose age was ≥ 18 years and who had undergone surgery in Sweden during 2017–2019 and the total population size in Sweden, attained from Statistics Sweden (www.scb.se).

Statistical Analysis

The Mann-Whitney U-test and Kruskal-Wallis test were used to compare two and more than two independent groups, respectively. The Pearson chi-square test was used to compare proportions, and the binomial test was used to compare surgery incidences. Statistical tests were two-tailed, and significance was set at $\alpha < 0.05$. For the systematic review, ordinary and weighted arithmetic mean values were calculated. The weights were proportional to

the sample size of each study. All statistical analyses were performed with PASW Statistics (version 25, IBM SPSS Statistics, IBM Corp.).

Ethical Considerations

The study was approved by the Swedish Ethical Review Authority. In accordance with Swedish legislation and regulations regarding patient consent for participation in a national quality registry, before undergoing surgery, patients are given written information about the SHQR including the choice to opt out from registration in the SHQR or for their data to be removed from the register at any time.

Systematic Review

The systematic review was done according to the *Cochrane Handbook for Systematic Reviews of Interventions*.[16] The search strategies were developed by two expert health librarians (Linda Hammarback, Eva Hessman) in close cooperation with one author (C.W.). The strategies focused on two main concepts: normal pressure hydrocephalus and demography and their association with related terms. The PubMed, Cochrane, and Scopus electronic databases were used on the basis of their scope corresponding with the subject in question. Searches of the electronic databases were all conducted on the same day, August 18, 2019, from database inception. No language restrictions were applied at this stage.

PubMed, Scopus, and Cochrane databases revealed 1070, 820, and 139 citations, respectively, using the terms presented in the *Appendix*. After removing duplicates, 1020 unique articles were identified and imported into the Rayyan tool for systematic reviews (https://rayyan.qcri.org/) for screening by reading the title and abstract (independently by L.A., N.S., and C.W.). Disagreements were resolved by discussion after the screening was completed. Thirty full articles were retrieved by three authors (L.A., F.L., and M.T.) on the basis of their pertinence and relevance to the topic of the review. Fourteen articles were excluded (3, non-English language; 1, retracted; 3, duplicates; and 7, wrong study area), and the remaining 16 articles were assessed (M.T., C.W., and F.L.) for quality and risk of bias using the Newcastle-Ottawa Scale for case-control studies, selection category (Table 2, Fig. 1).[17] Data were collected by N.S. and C.W.

Results

The mean age at the time of surgery among 3000 patients from the registry was 74.4 years (range 40–92 years) with the highest patient frequency (79%) in the span between 70 and 80 years (Fig. 2 upper). The mean age of the 10 subjects who had undergone ETV was 70.3 years (range 60.8–84.0 years). Men constituted 60.3% of the patients and women 39.7% ($p < 0.001$). Men and women were similarly aged ($p = 0.8$) at the time of diagnosis. Sixty-four patients (2%) were younger than 60, and only 1 patient was younger than 50 years. The median (IQR [quartile 1, quartile 3]) diagnostic delay was slightly longer for women (3, IQR 2, 4 years) than for men (2, IQR 1, 4 years); however, the difference between the two was not significant ($p = 0.58$). The median diagnostic delay was similar among the age groups (40 to < 60 years, 2 years; 60 to < 80, 3; 80 to < 85, 2; and ≥ 85, 2.5; $p = 0.81$).

Initial Symptoms

The initial symptoms reported were gait impairment (95% of patients), balance problems (95%), cognitive deterioration (75%), and urinary dysfunction (69%). The range of missing data for these categories was 3% (gait) to 8% (cognition). Only 14% of patients reported headache from the onset of disease (missing data 29%). Patients aged < 60 years reported more headaches (30% vs 14%, respectively; $p = 0.002$) and fewer balance problems (86% vs 95%, $p = 0.001$) than the patients aged ≥ 60 years.

All four main symptoms (i.e., issues with balance, gait, cognition, and urinary function) were present from disease onset in 48% of the patients (53% women, 45% men), three were in 32% (30%, 33%), two were in 15% (13%, 16%), and one was in 5% (4%, 6%). Fifty-six patients (2%) had initial symptoms in only the cognitive and/or continence domains. Initial symptoms were unknown in 2% of the patients.

Symptoms at the Time of Diagnosis

The typical iNPH patient presented with wide-based gait with sway (gait score 3), an ability to stand independently with the heels together (balance 3), frequent incontinence requiring a napkin (continence 4), and slight disability with no need for assistance (mRS score 2; Fig. 2 lower).

Standardized gait, balance, and continence scores and miNPH, MMSE, and mRS scores as well as the number of preoperative comorbidities are presented in Table 3. The performance on all of these measures decreased significantly with increasing age across all age groups, except from 80 to < 85 and ≥ 85 years for balance, continence, and MMSE. The number of comorbidities did not differ among age groups.

Figure 3 shows the relationship between the mRS and miNPH scores for women and men. When mRS scores were dichotomized (scores 0–2 and 3–5), the miNPH score was higher in patients with lower mRS scores ($p < 0.0001$). Women were more impaired in function than men at the time of diagnosis: the median preoperative miNPH score was 55.3 (IQR 37.0, 67.5) in women and 62.3 (IQR 44.8, 72.3) in men ($p < 0.001$).

In 47% of patients (n = 1142, data missing in 548 patients) the MMSE score was lower than 25, and in 39% of patients (n = 963, data missing in 548 patients) it was lower than 24. Of those patients aged ≥ 80 years, 57% had an MMSE score below 25. Patients with an mRS score ≤ 2 had a higher MMSE score (27, IQR 24, 28) than those with an mRS score ≥ 3 (23, IQR 19, 26; $p < 0.0001$).

When dichotomizing diagnostic delay (time in years from symptom onset to surgery) into ≤ 1 and > 1 year, there was no difference in the MMSE score (25, IQR 22, 28 vs 25, IQR 21, 28; $p = 0.23$) or miNPH score (59, IQR 41, 72 vs 59, IQR 41, 71; $p = 0.48$) between the two groups.

Comorbidities and ASA Status

The number of comorbidities was the same in the dif-

TABLE 2. Newcastle-Ottawa Scale for 16 case-control studies, selection category

Article No.	Authors & Year	NOS Selection: Case Definition	Represent	Selection of Controls	Definition of Controls	Overall NOS Selection Score	% Male	Age	Data Extracted for Meta-Analysis (no. of patients)
1	Andersson et al., 2019[41]†	*	*	*		***	60	>65 yrs probable, median 82.0 yrs (IQR 11)	Prevalence (673), sex (25)
2	Andrén et al., 2018[32]‡	*	*			**	58	Median 74 yrs (IQR 68–78)	Sex (979), vascular comorbidity (977), stroke (977)
3	Brean & Eide, 2008[6]†	*	*			**	52	50–80 yrs, highest incidence at 70–79 yrs	Prevalence (81), incidence (81), sex (48)
4	Hiraoka et al., 2008[40]§	*	*	*		***	60	5 patients btwn 69 & 82 yrs	Prevalence (170), sex (5)
5	Huovinen et al., 2016[38]‡	*	*			**	46	Mean at shunt surgery 70.3 yrs (SD 7.7)	Sex (375), BMI (375), vascular comorbidity (375), stroke (375)
6	Iseki et al., 2014[7]§	*	*	*	*	****	NA	Btwn 70 & 80 yrs, 3 patients developed iNPH	Incidence (271)
7	Israelsson et al., 2017[25]‡	*	*	*		***	58	60–85 yrs, mean 74 yrs (SD 6)	Sex (176), BMI (138), smoking (172), vascular comorbidity (138–157), stroke (146)
8	Jaraj et al., 2016[26]§	*	*	*		***	NA	Mean 84.9 yrs (SD 4)	Smoking (21), vascular comorbidity (21–23), stroke (23)
9	Jaraj et al., 2014[4]§	*	*	*		***	NA	Mean 85.3 yrs (SD 4)	Prevalence (1238)
10	Krauss et al., 1996[42]‡	*	*		*	***	46	Mean 70.8 yrs (SD 7.4)	Sex (65), smoking (49), vascular comorbidity (63–65), stroke (65)
11	Kuriyama et al., 2017[43]†	*	*			**	59	Mean at diagnosis 75.5 yrs (SD 8.6)	Sex (1524)¶
12	Martín-Láez et al., 2016[44]†	*	*			**	58	<60–85 yrs, highest incidence at 75–79 yrs	Incidence (293), incidence of surgery (6×10^6), sex (187)
13	Pyykkö et al., 2018[45]†	*	*			**	43	Median 73.3 yrs, range 43.5–87.9 yrs	Incidence (536), incidence of surgery (15.5×10^6), sex (283), vascular comorbidity (283)
14	Sundström et al., 2017[8]‡	*	*			**	58	Mean 72.4 yrs, range 30–90 yrs	Incidence of surgery (72×10^6), sex (1008)
15	Tanaka et al., 2009[3]§	*	*	*		***	71	>65 yrs, 7 patients; range 66–82 yrs	Prevalence (497), sex (7)
16	Tisell et al., 2005[5]‡	*	*			**	NA	Mean 67 yrs, range 18–88 yrs	Incidence of surgery (27×10^6)

Incidence = incidence of iNPH; NA = not available; NOS = Newcastle-Ottawa Scale; prevalence = prevalence of iNPH; Represent = representativeness.
Vascular comorbidity includes hypertension, diabetes mellitus, and heart disease. For incidence of surgery, the number was taken as the size of the study population times the number of years the study was conducted. The Newcastle-Ottawa Scale uses stars (here *) in its scoring.
† Based on survey.
‡ Based on operation.
§ Based on population.
¶ Since the nature of the study differs significantly from all others, iNPH prevalence (reported as 10.2/100,000 inhabitants) was not included in the ordinal and weighted mean values of this systematic review.

ferent age groups ($p = 0.60$; Table 3). Men had significantly more diabetes, heart disease, hypertension, and stroke than women (Table 4). When comorbidities were dichotomized into groups of 0–1 or 2–5, men had significantly more comorbidities than women; 43% of men and 28% of women had 2–5 comorbidities ($p < 0.0001$). Patients with fewer comorbidities had a significantly higher miNPH score: 0 or 1 comorbidities (n = 1544), miNPH score of 62 (IQR 43, 72); and patients with 2–5 comorbidities (n = 940), miNPH score of 55 (IQR 37, 67; $p < 0.001$).

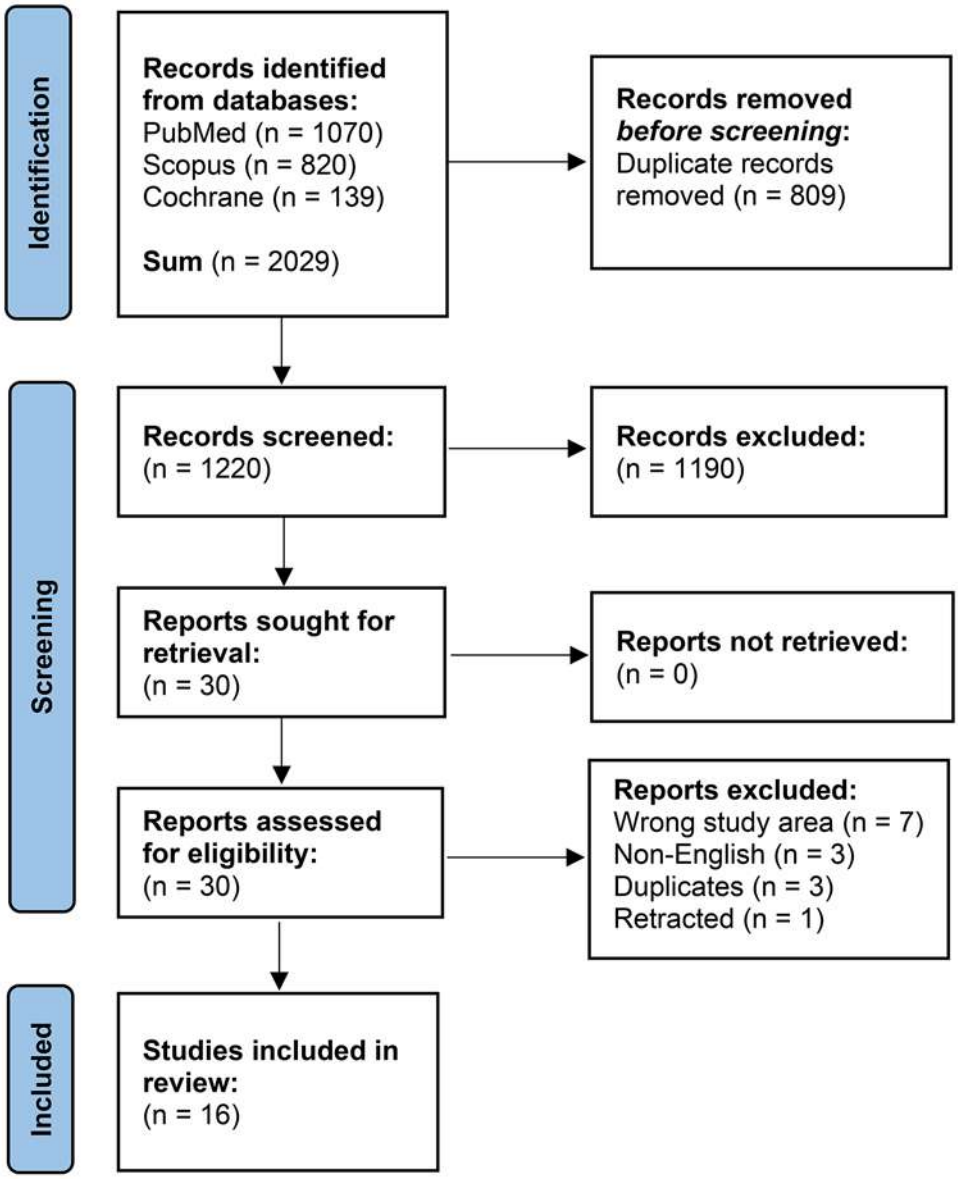

FIG. 1. PRISMA 2020 flow diagram. Data added to the PRISMA template (from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71). Figure is available in color online only.

ASA statuses are presented in Table 4. More men (49%) than women (44%) had an ASA class of III or IV ($p = 0.012$). Higher age was associated with a higher ASA class in both men and women. Sixty-seven percent of women and 52% of men aged ≥ 85 years had an ASA class of III or IV versus 54% of women and 30% of men younger than 60 ($p = 0.019$ and 0.023, respectively).

Systematic Review

All 16 studies had a clear case definition and good representativeness and were judged to have a low risk of bias (Table 2).

Numerical and weighted results differed because of sample size, with an iNPH prevalence of around 400/100,000 inhabitants (Table 5). The incidence of iNPH diagnosis was higher in population-based studies than in survey studies by a factor 10. The incidence of surgery was lower than the incidence of iNPH according to survey studies. The surgery incidence in the present study (years 2017–2019) was twice as high as the incidence in the other studies. Men were slightly overrepresented in most studies (Tables 2 and 5). Age could not be analyzed in detail given the large differences in the included age ranges among the different included studies, but there was without doubt a preference for age groups older than 60 years (Table 2). The frequency of hypertension and heart disease was highest in the survey-based studies, whereas the frequency of stroke was higher and diabetes mellitus lower in the

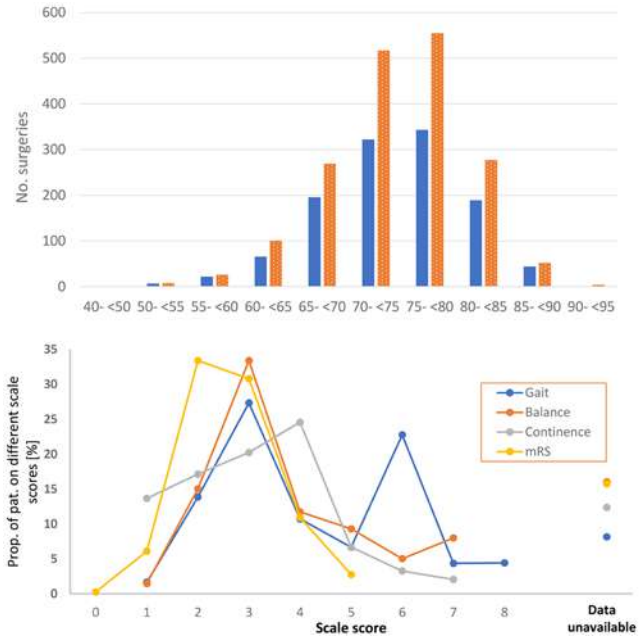

FIG. 2. Upper: Age and sex distribution of 3000 consecutive, surgically treated iNPH patients. Note the 5-year intervals on the x-axis, except for 40 to < 50 years. *Orange bars* represent men, and *blue bars* represent women. **Lower:** Ordinal scales of gait, balance, continence, and functional impairment (mRS) in 3000 iNPH patients. The x-axis corresponds to the levels/scores for each scale, whose meaning is explained in Table 1 (a higher score on the x-axis corresponds to more severe impairment). The proportion (%) of patients (pat.) having a certain score on each ordinal scale is shown on the y-axis. Farthest to the right, the frequency of unavailable data for each scale is shown. Figure is available in color online only.

population-based studies compared to the other types of studies. Weighted frequencies matched those found in the present study.

Discussion

This study, which was based on 3000 patients, showed that the typical iNPH patient is between 70 and 80 years old, presents with wide-based gait with sway, can stand independently with the heels together, is frequently incontinent to the extent of requiring a napkin, is cognitively disabled but seldom in need of assistance, and does not have headache. From a general perspective, iNPH is a debilitating disease with gait and balance disturbances causing immobility and an increased risk of falls as well as socially embarrassing urinary incontinence. Almost half of patients have an MMSE score below 25 and probably mild or severe dementia, further emphasizing that iNPH is important to diagnose and treat since it is one of very few treatable causes of dementia.[18]

The age distribution reported here is interesting. We used the international guidelines criteria for iNPH, with 40 years as the lower age limit for inclusion.[2] Only 64 patients (2%) were younger than 60, and only 1 was younger than 50 years. Even if it was not possible to calculate a mean age based on the systematic review, it is evident that it was well over 60 years (Table 2). The Japanese iNPH guidelines[9] have set the lower age limit for iNPH to 60 years, and a similar limit has also been recommended by others.[19] Interestingly, patients aged < 60 years reported more headaches and fewer balance problems than those aged ≥ 60 years. This profile has been described in the literature in younger patients with adult hydrocephalus and termed "syndrome of hydrocephalus in young and middle-aged adults" (SHYMA) or with "decompensated ventriculomegaly and early presenting ventriculomegaly" and "unrecognized congenital adult hydrocephalus."[19–21] These groups had, besides more frequent headaches, other symptoms such as nausea, vomiting, sleep pattern changes, and fatigue, which is unusual in elderly iNPH patients. This difference in symptom profile does not seem to relate to comorbidity, which was similar among the age groups in our study. Further, the patients younger than 60 years also presented with a significantly lower burden of the classic iNPH symptoms (Table 3). Together, these data compel us to suggest that 60 years old is a better lower limit for iNPH and should be generally recommended. Omitting patients younger than 60 will increase the homogeneity of the iNPH phenotype, with around 80% of the patients being in their 70s when operated on and 47% of them presenting with symptoms from all four domains.

The systematic review and large nationwide study indicate that more men than women (56% and 60%, respectively) are surgically treated for iNPH. Whether this also means that more men suffer from iNPH is debatable. Women and men were similarly aged at the time of diagnosis, but women had a slightly longer but not statistically significantly different diagnostic delay (i.e., duration between initial symptoms and operation). Unfortunately, this difference could not be further investigated because of the low resolution of years (as opposed to months). We considered asking patients for more precise time points of symptom onset, but because of the insidious nature of the disorder in combination with possible memory issues, the risk of receiving unreliable data was considered too high. Further, more women presented with the full tetrad of symptoms at the time of diagnosis and had lower miNPH scores by 11% than men at the time of diagnosis. Similar results were reported in a European multicenter study and the study by Andrén et al.[22,23] This may be attributable to a sex-related delay or absent development of iNPH symptoms and signs in women and possibly an underrepresentation of women with less pronounced symptoms. However, the lower miNPH score in women at the time of diagnosis could also partly be due to healthy women in the age span of interest having worse clinical performance in general, that is, 10%–15% lower gait speed.[24] The miNPH does not control for this sex-related difference in gait.[11]

The most probable explanation for the sex-related difference in iNPH operation frequency is the association between vascular risk factors in iNPH and the higher occurrence of these risk factors in men,[25,26] even when the increase in vascular comorbidities in women after menopause is taken into account.[27] In this study, 43% of the men had 2–5 comorbidities, whereas only 28% of women had similar numbers. In population studies of healthy elderly patients, the prevalence of comorbidities and number of comorbid conditions increased with age,[28] and 24% of

TABLE 3. Preoperative gait, balance, continence, miNPH, MMSE, and mRS scores and number of comorbidities in 3000 surgically treated iNPH patients

Variable	All Patients*	Age Interval†			
		40 to <60 yrs	60 to <80 yrs	80 to <85 yrs	≥85 yrs
Gait scale					
Median score (IQR), no. of patients	57 (29.0, 71.0), 2755	71.0 (29.0, 86.0), 56	71.0 (29.0, 71.0), 2161	43.0 (29.0, 71.0), 438	29.0 (29.0, 57.0), 100
p value	**0.000**				
60 to <80 yrs		**0.030**			
80 to <85 yrs		**0.000**	**0.000**		
≥85 yrs		**0.000**	**0.000**	**0.002**	
Balance scale					
Median score (IQR), no. of patients	67 (33.0, 67.0), 2519	67 (50.0, 83.0), 52	67 (50.0, 67.0), 1972	50 (33.0, 67.0), 402	50 (17.0, 67.0), 93
p value	**0.000**				
60 to <80 yrs		**0.017**			
80 to <85 yrs		**0.000**	**0.000**		
≥85 yrs		**0.000**	**0.000**	0.113	
Continence scale					
Median score (IQR), no. of patients	60 (40.0, 80.0), 2629	60 (60.0, 90.0), 53	60 (40.0, 80.0), 2068	50 (40.0, 80.0), 418	60.0 (40.0, 80.0), 90
p value	**0.004**				
60 to <80 yrs		**0.018**			
80 to <85 yrs		**0.002**	**0.012**		
≥85 yrs		**0.01**	0.324	0.735	
miNPH					
Median score (IQR), no. of patients	58.8 (41.3, 71.3), 2670	67.3 (46.8, 80.9), 54	60.7 (42.0, 72.3), 2092	51.2 (32.8, 67.3), 428	46.3 (32.8, 60.8), 96
p value	**0.000**				
60 to <80 yrs		**0.005**			
80 to <85 yrs		**0.000**	**0.000**		
≥85 yrs		**0.000**	**0.000**	**0.037**	
MMSE scale					
Median score (IQR), no. of patients	25.0 (21.0, 28.0), 2458	27.0 (23.0, 29.0), 50	25.0 (22.0, 28.0), 1926	24.0 (20.0, 27.0), 395	23.0 (20.0, 27.0), 87
p value	**0.000**				
60 to <80 yrs		**0.016**			
80 to <85 yrs		**0.000**	**0.000**		
≥85 yrs		**0.000**	**0.001**	0.23	
mRS					
Median score (IQR), no. of patients	3.0 (2.0, 3.0), 2528	2.0 (2.0, 3.0), 54	2.0 (2.0, 3.0), 1986	3.0 (2.0, 3.0), 397	3.0 (3.0, 4.0), 91
p value	**0.000**				
60 to <80 yrs		**0.006**			
80 to <85 yrs		**0.000**	**0.000**		
≥85 yrs		**0.000**	**0.000**	**0.019**	
Comorbidities					
Median no. (IQR), no. of patients	1.0 (0.0, 2.0), 2612	1.0 (0.0, 2.0), 54	1.0 (0.0, 2.0), 2067	1.0 (0.0, 2.0), 404	1.0 (0.0, 2.0), 87
Median score (IQR), no. of patients	0.061				

Gait, balance, and continence scale scores according to Table 1 were converted to a minimum-maximum range from 0 to 100, where 0 denotes the most severe dysfunction and 100 is the performance of an age-matched healthy population. Boldface type indicates statistical significance.

* Kruskal-Wallis test.

† Mann-Whitney U-test.

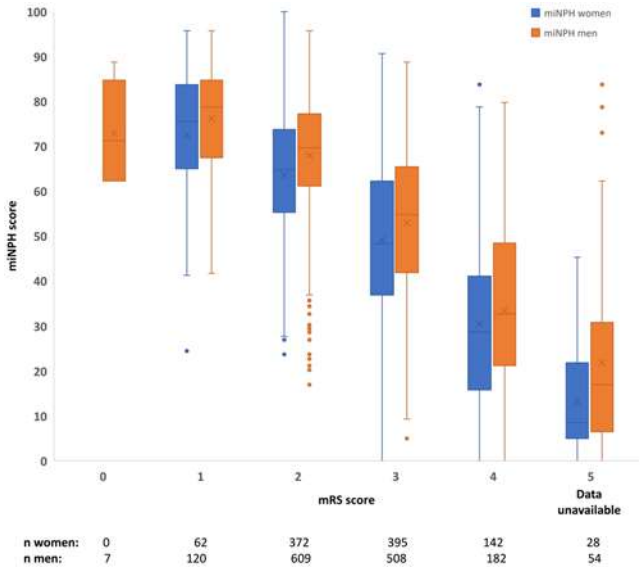

FIG. 3. Proportion of patients with preoperative miNPH scores on each level of the mRS for men and women. Farthest to the right, the frequency of missing data for each scale is shown. Figure is available in color online only.

Medicare beneficiaries, aged 65 years or older, had 4 or more chronic conditions.[29] The higher burden of comorbidity in iNPH patients compared to reference populations is associated with a worse physical condition and may negatively influence outcome,[30,31] but not to a degree that should inhibit treatment.[32]

The number of comorbidities did not differ among age groups; however, as expected, function in all domains decreased significantly with increasing age. This decrease may be attributable to a general age-related deterioration: gait velocity remains stable until about the age of 70, but after that, performance declines approximately 15% for normal gait and 20% for fast walking per decade.[33] However, iNPH patients aged ≥ 80 years in this study had a 40% or lower gait score than those in their 70s; therefore, our observation is probably not explained by age-related deterioration alone. One reason could be that the diagnosis of iNPH in patients older than 80 requires considerably more severe symptoms and signs to be distinguishable in the clinical setting from the possible effects of aging. Another reason could be that concomitant disorders lead to faster deterioration in older patients.

The most frequent time delay from initial symptoms to surgery was 2 years, and 2.6% of patients (73 patients) had a diagnostic delay of 11 years or more. A diagnostic delay of 2 or more years causes irreversible deterioration[34] and should be avoided. Even though deterioration can be insidious and slow, when symptoms and signs are typical, iNPH should be suspected, investigated, and probably treated.

According to our systematic review, the prevalence of iNPH is slightly higher than 400/100,000 inhabitants, equivalent to 2% of people older than 65 years. The reported incidence is less than 5% of the prevalence, and only 20% of those diagnosed are operated on (Table 5). These are alarming data from a humanitarian point of view, and efforts are greatly needed to change this situation. Moreover, the socioeconomic consequences are devastating considering the clinical efficiency[35] and high cost-effectiveness of shunt op-

TABLE 4. Frequency of comorbidities and ASA classes

Variable	No. (%)			p Value (women vs men)
	Total	Women	Men	
Comorbidity				
Hypertension	1612 (58)	593 (53)	1019 (61)	**0.001**
Heart disease	807 (29)	220 (20)	587 (36)	**<0.001**
Diabetes mellitus	717 (26)	230 (21)	487 (30)	**<0.001**
History of stroke	278 (14)	106 (10)	272 (17)	**<0.001**
Intermittent claudication	44 (2)	18 (2)	26 (2)	0.94
No. of comorbidities*				
0	785 (29)	397 (37)	388 (25)	
1	877 (33)	378 (35)	499 (32)	
2	669 (25)	225 (21)	444 (28)	
3	268 (10)	71 (7)	197 (13)	
4–5	42 (2)	7 (1)	35 (2)	
ASA class†				
I	102 (4)			
II	1293 (49)			
III	1198 (46)			
IV	23 (1)			

* Patients with an unknown status for more than one comorbidity were excluded from the comorbidity summation (n = 359).
† Missing data for ASA class = 384 subjects.

TABLE 5. Summary of demographic data from the 16 studies categorized by study design: survey, population based, and operation based

Variable	Based on Survey		Based on Population		Based on Operations		All Studies		Present Study
	Ordinary*	Weighted*	Ordinary*	Weighted*	Ordinary*	Weighted*	Ordinary	Weighted	
Prevalence of iNPH†	361	627[1,3]	427	387[4,9,15]			400	455	
Incidence of iNPH†	3.5	2.6[3,12,13]	30[6]				10.2	8.9	
Incidence of surgery	2.2	2.0[12,13]			1.6	1.7[14,16]	1.9	1.7	3.7
% men	53	56[1,3,10–13]	66	66[4,15]	55	56[2,5,7,14]	56	56	60
% smoking	24[10]		19[8]		55[7]		33	46	
BMI					29	29[5,7]	29	29	
% w/ hypertension	83	83[10,13]	43[8]		63	54[2,5,7]	66	59	58
% w/ diabetes	36	28[10,13]	13[8]		28	25[2,5,7]	28	25	26
% w/ heart disease	38	25[10,13]	18[8]		21	23[2,5,7]	26	23	29
% w/ stroke	22[10]		57[8]		18	15[2,5,7]	26	16	14

Ordinary and weighted mean values are given for each variable and summarized for all.

* Superscripted numbers refer to article numbers listed in Table 2.

† Prevalence and incidence are given as numbers per 100,000 inhabitants.

erations.[36] Awareness of iNPH among both nonprofessionals and health professionals should be augmented.

The incidence of shunt surgery for iNPH in Sweden has increased continuously since the registry was started in 2004: from 1.0/100,000 inhabitants in 2004 to 3.7/100,000 in 2017–2019. The present Swedish incidence is twice that found in the systematic review, and we are confident that the increased awareness of iNPH after starting the registry is one important reason for this increase.

The prevalence of comorbidities was nearly the same in the systematic review and our study, except for a higher prevalence of hypertension in the survey studies and somewhat higher incidence of stroke. Greater comorbidity correlated with a worse miNPH score, further emphasizing the urgency in treating these factors. Body mass index (BMI) is rather seldomly registered in iNPH studies, but obesity is a known risk factor for overall mortality and vascular disease[37] and thus is as important to register as other risk factors. In the systematic review, two studies reported a BMI of 29,[25,38] which falls within the overweight range.

Gait and balance impairments are the most common initial symptoms according to both the systematic review and our study, in which 95% of patients reported initial gait and/or balance disturbance. Slightly less frequent were cognitive deterioration (75%) and urinary dysfunction (69%). As in a European multicenter study,[22] the number of patients with the full triad or tetrad was approximately 50%. It could be even higher because of reporting bias: all symptoms may have appeared at the same time but were observed or reported in a specific order depending on the ease with which they could be articulated or the level of associated embarrassment. According to our experience, patients must be specifically asked about bladder problems, as these symptoms are seldom spontaneously reported. Relatedly, many patients blame old age for their cognitive difficulties and therefore do not talk about them or feel embarrassed or simply neglect these problems.

Overall, 963 patients (39%) had an MMSE score lower than 24 and 1142 patients (47%) had a score lower than 25 and would therefore probably have been diagnosed with mild or severe dementia.[18] The MMSE score was highly dependent on age and, as expected, related to patient functional ability level as assessed by the mRS: patients with an mRS score ≤ 2 had a higher MMSE score (median 27, IQR 24, 28) than those with an mRS score ≥ 3 (23, IQR 19, 26; $p < 0.0001$). According to the World Health Organization (WHO), the estimated proportion of the general population aged 65 and above with dementia at a given time is between 5% and 8%. If approximately 2% of those older than 65 years suffer from iNPH and 39%–47% of that population is demented, then iNPH accounts for at least 10%–15% of all cases of dementia. Therefore, we believe that it is very problematic that the WHO does not mention iNPH in their description of causes of dementia (https://www.who.int/news-room/fact-sheets/detail/dementia).

Only 14% of patients reported headache at disease onset. The prevalence of headache in the general population older than 65 in Italy was 51%,[39] considerably higher than in our study, clearly documenting that headache is an uncommon symptom in elderly iNPH patients. ASA statuses were higher in the elderly, indicating that they were affected by ailments to a considerably greater degree than younger persons. Our data, however, do not indicate that the elderly are refused treatment because they are more affected by disease.

Strengths and Limitations

There are limitations to performing registry-based studies. For example, there is always the risk that procedures will change over time, in this case 15 years, which is why we adopted quantitative data collection as much as possible. Procedures can also differ between sites, and to minimize such differences, only one or two administrative persons per site are responsible for all registrations, and regular meetings to agree on variable definitions and registration techniques, as well as regular site inspections, are held. Two centers could not participate in the SHQR for all 15 years because of administrative difficulties; however, national coverage is still very high in the registry, and

we do not think that this affected the results of our study. Registry-based studies also offer unique opportunities to address research questions on the basis of large groups of consecutively included data. These data represent the daily clinical situation, without the selection bias generally affecting more specialized studies, and thus represent the iNPH population in a way that is hard to achieve by prospective study inclusion.

The number of papers describing demographic data were few and divergent regarding several parameters, for example, the prevalence of hypertension and diabetes, with survey studies reporting very high levels for both. To interpret these differences is difficult, but as the population- and operation-based studies using other methodologies are more congruent, we believe them to be more reliable. However, it is regrettable that stronger descriptive measures could not be found even when all studies from the literature were included. We cannot rule out that the limitation in our systematic review of normal pressure hydrocephalus and demography excluded some studies investigating, for example, vascular comorbidity, smoking, or BMI. Nonetheless, we believe that these variables are most commonly included in larger contexts, which is why they are likely to be captured when studying demography.

We chose to present both ordinary and weighted mean values. Which mean value is more representative is difficult to know; the weighted mean enhances the results of larger studies with supposedly more power, whereas the outcome of smaller, perhaps well-implemented, studies is suppressed. The ordinary mean, on the other hand, treats all studies equally regardless of size, which may not always be reasonable or representative.

Conclusions

iNPH patients experience long diagnostic delays and have very low incidences of diagnosis and treatment. Very few iNPH patients are younger than 60 years of age, presenting with a slightly different symptomatology and probably a specific disease entity, indicating that the lower limit for iNPH should be 60 years. iNPH patients probably account for a considerable portion of all cases of dementia; therefore, iNPH is a very important disorder to diagnose and treat appropriately given the successful result expected.

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Appendix

PubMed identified 1070 citations using the following terms: (“hydrocephalus, normal pressure” [MeSH Terms] OR “normal pressure hydrocephalus” [tiab] OR NPH [tiab] OR “hakim syndrome” [tiab] OR “iNPH” [tiab] OR “hydrocephalic” [tiab] OR “normotensive hydrocephalus” [tiab] OR “adult hydrocephalus syndrome” [tiab]) AND (“Demography” [mesh] OR “demography” [tiab] OR “prospective studies” [mesh] OR “demographic” [tiab] OR “demographies” [tiab] OR “epidemiology” [mesh] OR “epidemiology” [tiab] OR “epidemiology” [subheading] OR “epidemiologic” [tw] OR “prevalence” [mesh] OR “prevalence” [tiab] OR “incidence” [mesh] OR “incidence” [tiab] OR “population-based” [tiab])

Scopus identified 820 citations using the following terms: (“hydrocephalus normal pressure” OR “normal pressure hydrocephalus” OR “NPH” OR “hakim syndrome” OR “iNPH2” OR “hydrocephalic*” OR “normotensive hydrocephalus” OR “adult hydrocephalus syndrome”) AND (“Demography” OR “demographic” OR “demographics” OR “epidemiology” OR “prevalence” OR “incidence”)

Cochrane identified 139 citations using the following terms: ([mh “hydrocephalus, normal pressure”] OR “normal pressure hydrocephalus” OR “NPH” OR “hakim syndrome” OR “iNPH” OR “hydrocephalic” OR “normotensive hydrocephalus” OR “adult hydrocephalus syndrome”) AND ([mh “Demography”] OR “demography” OR “demographic” OR “demographies” OR [mh “epidemiology”] OR “epidemiology” OR [mh “prevalence”] OR [mh “incidence”])

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Author Contributions

Conception and design: Sundström, Wikkelsø. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Sundström, Wikkelsø. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sundström. Statistical analysis: Sundström. Study supervision: Wikkelsø.

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