scientific reports

Check for updates

OPEN

# Brain and intracranial volumes are both enlarged and serve as potential risk factors in normal pressure hydrocephalus

Dylan Hoyt[1], Clay M. Oliver[2], Raza Mushtaq[3], Jacob J. Knittel[2], Emily Foldes[3], Maddie Muenzer[4], Molly M. McElvogue[3], Daniel A. Keesler[1], J. Gordon McComb[5], Justin L. Hoskin[6] & Kevin S. King[2,3]✉

**Normal pressure hydrocephalus (NPH) is a poorly understood neurodegenerative condition leading to gait impairment and ultimately dementia. Prior work has shown larger intracranial volume (ICV) among those with NPH which has been taken to establish a link to Benign external hydrocephalus of infancy (BEH) as a predisposing factor. These studies have not evaluated brain volume which we hypothesize will also be elevated in NPH and account for the increase in ICV. Automated analysis was performed on CT head examinations from 305 NPH patients and 294 controls. Brain volume was ~ 4.8% larger in females ($p < .001$) and ~ 2.5% larger in males ($p = .003$) in NPH compared with controls and ICV was ~ 5.2% larger in females ($p < .001$) and ~ 3.7% larger in males ($p < .001$) with NPH compared with controls. The ratio of brain volume to intracranial volume in NPH versus controls was not significantly different for females ($p = .4$) or males, ($p = .08$). If BEH is a major cause of NPH this would then require that it also results in persistently enlarged brain volumes. Our data suggests large brain size itself is a risk factor for NPH and may help account for increased NPH risk among males.**

Normal pressure hydrocephalus (NPH) is a highly prevalent and potentially treatable neurodegenerative disease leading to gait impairment as well as dementia and incontinence[1]. The disease was first described by Hakim in 1964 and brought to wide attention with publication in the New England Journal of Medicine[2,3]. The prevalence of NPH increases with age, reaching 6–9% in those over age 80, with estimates surpassing 700,000 cases in the United States and 2,000,000 cases in Europe[4] though the disease is unfortunately underdiagnosed[5].

The etiology of NPH remains unknown. Bradley and Kreft reasoned that if NPH originated in adulthood after the cranial sutures fuse, the intracranial volumes would be like those of their healthy age- and sex-matched counterparts and thus took the larger head size in NPH as evidence that it was linked to hydrocephalus earlier in life. Prior studies led separately by Bradley and Kreft showing larger head sizes in NPH have been taken to suggest that NPH in adults is linked to benign external hydrocephalus of infancy (BEH)[6,7]. The predominant theory for BEH has suggested it to be the result of immature arachnoid villi in infants being unable to resorb cerebrospinal fluid (CSF) and maintain balance with CSF production. The resultant mismatch in BEH patients causes an accumulation of CSF leading to elevated intracranial volumes at a time when the cranial sutures are unfused and head size becomes enlarged[8,9]. Arachnoid villi are thought to mature by 18 months of age, at which point CSF no longer accumulates but head circumference is left markedly increased[10]. Reversible dural venous sinus outflow stenoses has also been suggested as a predisposing factor for BEH[11].

The theory linking benign external hydrocephalus with NPH postulates that these patients remain relatively asymptomatic until their elderly years, but their earlier condition evidences an inherent deficiency in CSF resorption. Bradley et al. proposed the idea of NPH as a "two-hit" disease beginning with benign external hydrocephalus in infancy coupled with the onset of senescent changes such as deep white matter ischemia in late adulthood that cause the disease to re-manifest[12]. Counter to this theory is additional clinical research be Wilson et al. evaluating the prevalence of enlarged head size in NPH compared with controls which suggested that benign external hydrocephalus may serve as the "first hit" in only a small subset of individuals[13].

[1]Department of Radiology, Creighton University, Phoenix, AZ, USA. [2]College of Medicine, Creighton University, Phoenix, AZ, USA. [3]Department of Neuroradiology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd, Phoenix, AZ 85013, USA. [4]Arizona State University, Tempe, AZ, USA. [5]Department of Neurosurgery, Children's Hospital Los Angeles, Los Angeles, CA, USA. [6]Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA. ✉email: Kevin.King@barrowneuro.org

| | Total ($N=599$) | NPH ($N=305$) | Control ($N=294$) |
|---|---|---|---|
| Age (Y) | 75.0 ± 7.6 | 75.9 ± 6.9 | 74.1 ± 8.2 |
| Sex | | | |
| Male | 364 (61%) | 195 (64%) | 169 (57%) |
| Female | 234 (39%) | 110 (36%) | 125 (43%) |

**Table 1**. Cohort characteristics, as mean and standard deviation for age and number and percentile for sex.

| | ICV (liter) | | | Brain (liter) | | | Brain/ICV | | |
|---|---|---|---|---|---|---|---|---|---|
| | Estimate | Std Error | Prob | Estimate | Std Error | Prob | Estimate | Std Error | Prob |
| Female | -0.1766 | 0.0097 | < 0.0001 | -0.1561 | 0.0085 | < 0.0001 | 0.02% | 0.36% | 0.965 |
| Age | 0.0003 | 0.0006 | 0.609 | -0.0022 | 0.0006 | < 0.0001 | -0.19% | 0.02% | < 0.0001 |
| NPH | 0.0570 | 0.0095 | **< 0.0001** | 0.0419 | 0.0084 | **< 0.0001** | -0.67% | 0.36% | **0.059** |

**Table 2**. Multiple linear regression analysis for determinants of intracranial volume (ICV), brain volume and brain/ ICV ratio by NPH status with adjustment for age and sex. Significant values are in bold.

| | Female ($N=235$) | | | | | Male ($N=364$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control ($n=125$) | | NPH ($n=110$) | | | Control ($n=169$) | | NPH ($n=195$) | | |
| | Mean | Std Error | Mean | Std Error | Prob | Mean | Std Error | Mean | Std Error | Prob |
| ICV (liter) | 1.16 | 0.009 | 1.22 | 0.010 | < 0.0001 | 1.34 | 0.009 | 1.39 | 0.009 | < 0.0001 |
| Brain (liter) | 1.03 | 0.008 | 1.08 | 0.009 | < 0.0001 | 1.20 | 0.008 | 1.23 | 0.008 | 0.0025 |
| Brain/ICV | 89.0% | 0.4% | 88.3% | 0.4% | 0.36 | 89.5% | 0.3% | 88.2% | 0.3% | 0.079 |

**Table 3**. Mean differences for NPH versus control stratified by sex.

The purpose of this study is to further evaluate enlarged intracranial volumes of patients by also evaluating brain volumes to determine if there is discrepancy as would be expected in the setting of enlarged head size related to hydrocephalus from infancy. Benign external hydrocephalus results in elevated CSF and intracranial volumes as seen in NPH but it is not known if this could account for an elevation in brain volume. In this work we evaluate the hypothesis that there is a concordant increase in brain volumes and head size between NPH patients and controls.

## Results

Demographic information for our cohort is shown in Table 1.

After age and sex matching, the control and NPH groups showed no significant difference in sex (T- test $p=.11$). The mean age was statistically slightly different with mean control age being 1.8 years younger than for NPH (T-test, $p=.0004$). Outcome of multiple linear regression analysis of the entire sample for determinants of ICV and Brain volumes and Brain/ ICV ratio with Sex, Age, and NPH status as predictors is shown in Table 2. Both intracranial volume (ICV) and Brain volume were significantly larger in NPH versus control ($p<.0001$) but Brain/ICV ratio did not reach significance ($p=.06$). Results for linear regression stratified by sex and with adjustment for age are shown in Table 3. Briefly, intracranial volume for patients with NPH was ~ 5.2% larger in females and ~ 3.7% larger in males than that seen in controls. Brain volume was also ~ 4.8% larger in females and ~ 2.5% larger in males in NPH compared with controls. The ratio of brain volume to ICV was not statistically significant overall but there was a sex difference with suggestion towards a trend among males.

Observed values for ICV, brain volumes and brain/ICV ratio were found to be identical to age adjusted means to 3 significant digits; these observed values and are shown in Fig. 1. This showed was a slightly larger increase in brain volumes for females with versus without NPH at 0.05 compared with the difference for men at 0.03.

## Discussion

Our study confirmed our hypothesis and showed that brain volumes as well as ICV is enlarged among a large ($n=305$) cohort with NPH ($p<.001$) and that the ratio of Brain volume to ICV is not significantly different. This study add important information to prior influential works led by Bradley and Kraft in smaller cohorts which had previously found enlarged head size and ICV in NPH and had used this to establish a link between NPH and BEH[6,7]. These studies were not able to measure brain volumes, which have not yet been established to also be enlarged in BEH patients into adulthood.

Our findings have important implications for interpreting the findings in prior NPH studies by Bradley and Krefft which have had a significant impact on our understanding of the disease. Based on increased ICV

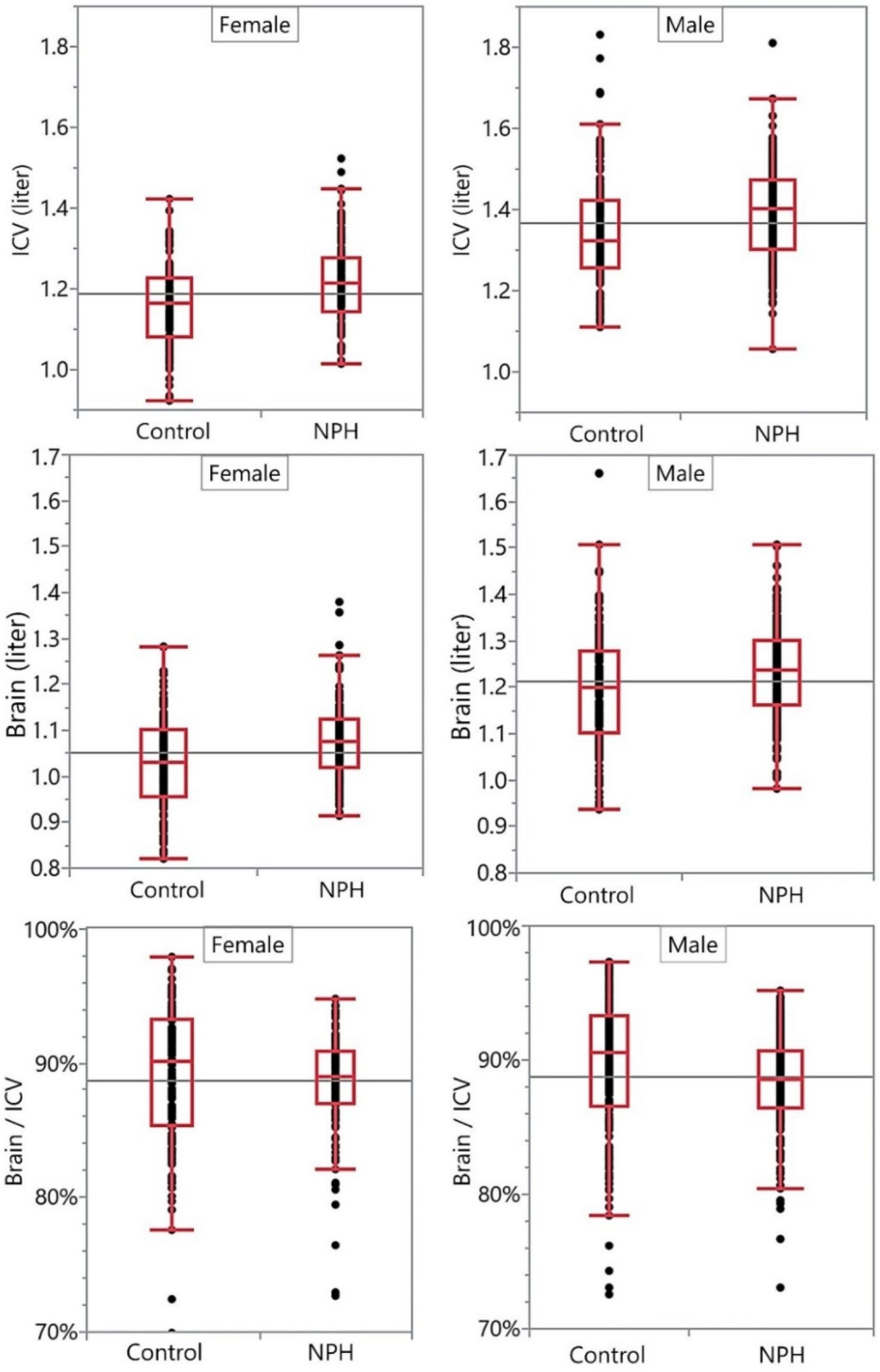


**Fig. 1**. Distribution of Intracranial Volume (ICV), Brain Volume, and Brain / ICV ratio for Control versus NPH stratified by sex.

among those with NPH, these studies have been widely touted as supporting BEH in infancy as an important risk factor for development of NPH later in life. These studies helped establish the theory of NPH as being a "two-hit" disease, beginning with BEH coupled with the onset of deep white matter ischemia in late adulthood[12]. This theory suggests the presence of an innate deficiency in CSF resorption manifests in infancy as benign external hydrocephalus and later in life, with a second hit from accumulation of age-related microvascular insults, results in NPH. This theory has had important implications for directing research efforts to identify

underlying mechanisms. The enlargement of brain volumes congruent to head size amongst patients with NPH is an important observation. Work is now needed to determine if brain volumes remain elevated in patients with BEH to determine if there is plausible link between BEH and NPH.

There is some support in the literature for a possible persistent increase in brain volumes in BEH. Bateman has proposed venous outflow stenoses to be a risk factor for the development of benign external hydrocephalus. A 10-year review of MRI findings in children with suspected idiopathic intracranial hypertension by Bateman et al. in 2020 points out a 9% increase in brain volume amongst patients at risk for idiopathic intracranial hypertension[14]. Venous outflow stenoses has been a known contributor to intracranial hypertension. If venous outflow stenoses is a factor contributing to the development of both pediatric idiopathic intracranial hypertension and benign external hydrocephalus, it is possible that both diagnoses may lead to elevated brain volumes. If infants with benign external hydrocephalus do, in fact, have enlarged brain volumes persisting into late adulthood, our findings agree that such patients would be at risk for developing NPH. As evidenced by this observation, it is important to keep in mind the many potential sources which may lead to elevated brain volumes.

Even if brain volumes do not also remain elevated in patients with BEH there would remain a possible link to pediatric hydrocephalus among a subset of those with NPH as has been suggested in clinical studies by Wilson et al.[13]. While we found that the ratio of brain volume to ICV is not significantly different overall, there is a possible trend ($p = .06$) which further analysis showed to be primarily among men ($p = .08$) compared with women ($n = .4$). This is intriguing as BEH is seen primarily in males[15] and may therefore support continued exploration of links with NPH among a subset, as has been suggested from the prior work by Wilson et al. It should be noted, however, that other processes may also account for differences in ICV discordant from brain volume. Recent work has challenged the presumption of fixed ICV in adulthood[16]. Other dementias such as Alzheimer's disease, which may co-exist with NPH, have also been linked to increased ICV, particularly in males[17]. Longitudinal analysis may likely be required to distinguish between these potential causes.

An intriguing possibility from our study is that enlarged brain volume itself (with concordant increase in head size) may be a risk factor for NPH. This may help explain the increased risk of NPH among men; brain volumes and head size are larger among males, predominantly related to a corresponding increase in height[18]. Further, more than 10% of women in our control sample had brain volumes of 0.9 L or less but none of the women with NPH (or any of the men in either the control or NPH groups) had brain volumes of this size. A recent study found evidence for inherited risk for NPH implicating the presence of genetic factors[19] which may potentially be associated with or cause differences in brain volume. Further work is needed to evaluate how larger brain volumes are linked with the development of NPH and how these may relate to genetic risk and the increased prevalence among men.

The study acknowledges a few limitations. As a cross sectional study we establish correlations but cannot establish causality. Larger brain volumes were seen in NPH, but this may be due to other linked factors we have not evaluated. While we attempted age matching, due to differences in our available control group, we were left with a slight but statistical difference of 1.8 years and as a result we therefore also adjusted for age in our statistical analysis. Finally, brain volumes and ICV vary depending on imaging modality and small differences are to be expected when comparing our values to those obtained from MRI[20]. This does not detract from the validity of the differences we observe here where only CT are used.

In conclusion, our findings demonstrate a concordant elevation of both brain and intracranial volumes among patients with NPH compared to healthy controls. This adds important new information to a common theory attributing increased head size seen in NPH to Benign External Hydrocephalus of infancy earlier in life, as this has not yet been established to result in increased brain volumes into adulthood. Our data raises the intriguing possibility that large brain size itself may be a risk factor for NPH and offers insights higher susceptibility for NPH among males.

## Methods

This study was approved by the St. Joseph's Hospital and Medical Center - Dignity Health Institutional Review Board (IRB), NUMBER: PHX-22-500-120-30-04, first approved Aug. 2021. As a low-risk retrospective study we were granted a waiver of informed consent by our IRB to conduct this study using a deidentified dataset. All methods were carried out in accordance with relevant guidelines and regulations.

### Cohort

We evaluate a cohort of 599 with 294 control patients and 305 NPH patients. Patients with probable NPH from our Normal Pressure Hydrocephalus Clinic who showed objective improvement on gait testing following a tap test and that had pre-operative CT WAND studies between the dates of January 2015 and January 2022 were included. Further, patients included in this cohort are presumed to have idiopathic NPH based on absence of history and of imaging findings for other known causes of hydrocephalus such as prior hemorrhage, major traumatic brain injury, or known congenital abnormality. Our clinic has established guidelines for the diagnosis of probable NPH in accordance with American Academy of Neurology guidelines[21] and the international guidelines proposed by Relkin[1]. In addition to utilizing a combination of patient features, exclusion of other diagnoses and pertinent imaging findings, this also includes responsiveness on objective gait testing following CSF tap-test[21]. Each patient undergoing a CSF tap test undergoes an objective gait measurement exam 4–10 days prior to the tap test. On the day of the tap test, fluoroscopic guidance is utilized to remove 30 ml of CSF. The patient is re-tested using the same set of gait measurement exams following the removal of CSF. Only patients who experienced responsiveness on objective gait measures were included in this study as probable NPH. On follow-up after shunting, included patients reported symptomatic improvement.

Controls were drawn from patients presenting to the emergency department with headache who had CT head exams performed with thin bone algorithm slice which were interpreted as negative. Age and sex matching were performed among a pool of 596 available controls, but perfect matching was not completely possible as discussed in the results and with statistical adjustment for age and sex described in the statistics section. History of previous large-territory infarct, neoplasm, or significant trauma were excluded from the control group.

### CT imaging and analysis technique

The head CT image technique for the included patients was a non-contrast head CT with 1.2 mm slice thickness images obtained using the high spatial frequency bone algorithm which was routinely available from all our CT head images from the emergency department and for surgical planning. NPH patient CT images were acquired following a successful lumbar puncture test as part of surgical planning for shunt placement. Control patient CT images were acquired as part of an institution-wide emergency department protocol.

The automated image analysis for both NPH patients and control patients was identical. DICOM images were anonymized and converted to NIFTI imaging format using MRIcroGL (freely available for download at www.nitrc.org). Image analysis was then performed using the Functional Magnetic Resonance Imaging of the Brain Software Library, typically referred to as FSL[22], by modifying routines previously published for analysis of CT head images[23,24]. The process started with initial image reorientation and resampling to generate isotropic images of standard voxel sizes. Following denoising, bone and fat were removed using Hounsfield Unit thresholding. FSL's Brain Extraction Tool[25] was used to isolate intracranial contents. Image cleanup, minimizing attenuation differences about the skull base, was performed using the restore output of the FMRIB's Automated Segmentation Tool[26]. CSF and Brain tissue masks were obtained using further thresholding with a Hounsfield Unit threshold of 20 based on empirical review for accuracy using masks overlayed on the CT images by an experienced neuroradiologist. Intracranial, brain, and CSF volumes were derived.

### Statistical analysis

Analysis was performed using JMP version 17 (SAS, North Carolina). Statistical significance was set at 0.05 using two tailed tests. Differences in age and sex between our control and disease (NPH) cohort were evaluated with T-tests. Multiple linear regression was performed to evaluate influence of NPH status on intracranial volume, brain volume, and brain to intracranial volume ratio with adjustment for age and sex. Female Sex and NPH were coded as numeric dummy variables of 1 with Male Sex and Control coded as 0. Mean differences for NPH versus control were then evaluated stratified by sex with adjustment for age using linear regression.

## Data availability

The datasets generated and/or analysed during the current study are not publicly available due to the guidelines of our IRB for retrospective analysis of patient data with waiver of informed consent. We are happy to provide our code on request so that our findings can be replicated on other datasets. Please contact the corresponding author Kevin King at Kevin.King@BarrowNeuro.org.

Received: 30 October 2024; Accepted: 3 March 2025
Published online: 08 March 2025

## References

1. Relkin, N., Marmarou, A., Klinge, P., Bergsneider, M. & Black, P. M. Diagnosing idiopathic normal-pressure hydrocephalus. *Neurosurgery* **57**, S4-16. https://doi.org/10.1227/01.neu.0000168185.29659.c5 (2005) (discussion ii-v).
2. Wallenstein, M. B. & McKhann 2nd, G. M. Salomón Hakim and the discovery of normal-pressure hydrocephalus. *Neurosurgery* **67**, 155–159. https://doi.org/10.1227/01.neu.0000370058.12120.0e (2010). discussion 159.
3. Adams, R. D., Fisher, C. M., Hakim, S., Ojemann, R. G. & Sweet, W. H. Symptomatic occult hydrocephalus with normal Cerebrospinal-Fluid pressure. A treatable syndrome. *N Engl. J. Med.* **273**, 117–126. https://doi.org/10.1056/NEJM196507152730301 (1965).
4. Jaraj, D. et al. Prevalence of idiopathic normal-pressure hydrocephalus. *Neurology* **82**, 1449–1454. https://doi.org/10.1212/wnl.0000000000000342 (2014).
5. Gavrilov, G. V. et al. Idiopathic normal pressure hydrocephalus (Hakim-Adams Syndrome): Clinical Symptoms, Diagnosis and Treatment. *Psychiatr Danub*. **31**, 737–744 (2019).
6. Bradley, W. G., Safar, F. G., Furtado, C., Ord, J. & Alksne, J. F. Increased intracranial volume: a clue to the etiology of idiopathic normal-pressure hydrocephalus? *AJNR Am. J. Neuroradiol.* **25**, 1479–1484 (2004).
7. Krefft, T. A., Graff-Radford, N. R., Lucas, J. A. & Mortimer, J. A. Normal pressure hydrocephalus and large head size. *Alzheimer Dis. Assoc. Disord.* **18**, 35–37. https://doi.org/10.1097/00002093-200401000-00007 (2004).
8. Kendall, B. & Holland, I. Benign communicating hydrocephalus in children. *Neuroradiology* **21**, 93–96. https://doi.org/10.1007/BF00342987 (1981).
9. Marino, M. A. et al. Benign external hydrocephalus in infants: A single centre experience and literature review. *Neuroradiol. J.* **27**, 245–250. https://doi.org/10.15274/NRJ-2014-10020 (2014).
10. Prassopoulos, P., Cavouras, D., Golfinopoulos, S. & Nezi, M. The size of the intra- and extraventricular cerebrospinal fluid compartments in children with idiopathic benign widening of the frontal subarachnoid space. *Neuroradiology* **37**, 418–421. https://doi.org/10.1007/BF00588027 (1995).
11. Bateman, G. A., Alber, M. & Schuhmann, M. U. An association between external hydrocephalus in infants and reversible collapse of the venous sinuses. *Neuropediatrics* **45**, 183–187. https://doi.org/10.1055/s-0033-1363092 (2014).
12. Bradley, W. G. Jr., Bahl, G. & Alksne, J. F. Idiopathic normal pressure hydrocephalus May be a two hit disease: benign external hydrocephalus in infancy followed by deep white matter ischemia in late adulthood. *J. Magn. Reson. Imaging.* **24**, 747–755. https://doi.org/10.1002/jmri.20684 (2006).
13. Wilson, R. K. & Williams, M. A. Evidence that congenital hydrocephalus is a precursor to idiopathic normal pressure hydrocephalus in only a subset of patients. *J. Neurol. Neurosurg. Psychiatry*. **78**, 508–511. https://doi.org/10.1136/jnnp.2006.108761 (2006).

14. Bateman, G. A., Subramanian, G. M., Yap, S. L. & Bateman, A. R. The incidence of obesity, venous sinus stenosis and cerebral hyperaemia in children referred for MRI to rule out idiopathic intracranial hypertension at a tertiary referral hospital: a 10 year review. *Fluids Barriers CNS*. **17**, 59. https://doi.org/10.1186/s12987-020-00221-4 (2020).
15. Zahl, S. M., Egge, A., Helseth, E. & Wester, K. Benign external hydrocephalus: a review, with emphasis on management. *Neurosurg. Rev.* **34**, 417–432. https://doi.org/10.1007/s10143-011-0327-4 (2011).
16. Caspi, Y. et al. Changes in the intracranial volume from early adulthood to the sixth decade of life: A longitudinal study. *NeuroImage* **220**, 116842. https://doi.org/10.1016/j.neuroimage.2020.116842 (2020).
17. An, H. et al. Large intracranial volume accelerates conversion to dementia in males and APOE4 non-carriers with mild cognitive impairment. *Int. Psychogeriatr.* **28**, 769–778. https://doi.org/10.1017/S104161021500229X (2016).
18. Scheffler, C., Greil, H. & Hermanussen, M. The association between weight, height, and head circumference reconsidered. *Pediatr. Res.* **81**, 825–830. https://doi.org/10.1038/pr.2017.3 (2017).
19. Greenberg, A. B. W. et al. Cases of Familial idiopathic normal pressure hydrocephalus implicate genetic factors in disease pathogenesis. *Cereb. Cortex*. **33**, 11400–11407. https://doi.org/10.1093/cercor/bhad374 (2023).
20. Nerland, S. et al. A comparison of intracranial volume Estimation methods and their cross-sectional and longitudinal associations with age. *Hum. Brain. Mapp.* **43**, 4620–4639. https://doi.org/10.1002/hbm.25978 (2022).
21. Halperin, J. J. et al. Practice guideline: idiopathic normal pressure hydrocephalus: response to shunting and predictors of response: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology. *Neurology* **85**, 2063–2071. https://doi.org/10.1212/WNL.0000000000002193 (2015).
22. Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W. & Smith, S. M. *FSL NeuroImage* **62**, 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015 (2012).
23. Muschelli, J. Recommendations for processing head CT data. *Front. Neuroinformatics*. **13**, 61. https://doi.org/10.3389/fninf.2019.00061 (2019).
24. Cauley, K. A., Och, J., Yorks, P. J. & Fielden, S. W. Automated segmentation of head computed tomography images using FSL. *J. Comput. Assist. Tomogr.* **42**, 104–110. https://doi.org/10.1097/rct.0000000000000660 (2018).
25. Smith, S. M. Fast robust automated brain extraction. *Hum. Brain. Mapp.* **17**, 143–155. https://doi.org/10.1002/hbm.10062 (2002).
26. Zhang, Y., Brady, M. & Smith, S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans. Med. Imaging*. **20**, 45–57. https://doi.org/10.1109/42.906424 (2001).


## Acknowledgements

This work was made possible by a grant from Rudi Schulte Research Institute in partnership with the Hydrocephalus Association supporting this work.

## Author contributions

The approval of all listed authors has been obtained for this submission. Each author had full access to the study data, participated actively in the analysis, and contributed to drafting and revising the manuscript. Particular contributions are as follows: Conceptualization and resources for the study were provided by KK with contributions from GM and JH. DH was primarily responsible for downloading and anonymizing images with assistance from CO, MM, MMM, DK and JK. RM and EF helped with supervision and methodology.

## Declarations

## Competing interests

The authors declare no competing interests.

## Additional information

**Correspondence** and requests for materials should be addressed to K.S.K.