Idiopathic intracranial hypertension: empowering patients and physicians to advance patient care through research

By

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Synopsis

Idiopathic Intracranial Hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP), papilloedema, with risk of permanent visual loss and chronic headaches. It predominately affects young women and is associated with obesity. The incidence of IIH is increasing as obesity rates increase, as confirmed in England analysing the Hospital Episode Statistic dataset.

Both physicians and patients are central to improving care and advancing knowledge. The first IIH consensus guidelines brought together a multidisciplinary group. A priority setting partnership was subsequently conducted and found a key knowledge gap that the Idiopathic Intracranial Hypertension Weight Trial (IIHWT) aimed to address.

The IIHWT found that bariatric surgery provided sustained ICP reduction and weight loss for up to two years. The per protocol analysis determined how much body weight should be lost to ensure disease remission. The IIHWT headache analysis uniquely found that ICP was correlated with headache outcomes. The pointwise visual field analysis demonstrated what could be a meaningful change in an IIH trial population.

The direct impact of this work has afforded a change in national guidelines for people living with obesity and IIH. The cumulative knowledge gained has now delivered the first international multidisciplinary research guideline for IIH.

Dedication

I am indebted to my father, Professor Raymond Alexander Boyce Mollan, an inspirational role model. He has patiently supported me through my career and in particular this research journey. His gentle guidance has allowed me to grow both as a clinician and as an academic.

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Working in partnership with Alex Sinclair to deliver this program of work has enabled us to propel IIH, a previously rare disease, into the lime light. The impact we have been able to deliver for this disease, I am sure will be evidenced for a long time.

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Abbreviations

ABN	Association of British Neurologists
BMI	Body mass index
CI	Confidence Interval
CSF	Cerebrospinal fluid
CT	Computerised Tomography
dB	Decibels
CWI	Community weight loss intervention
GLP-1	Glucagon-like peptide-1
HAD-A	Hospital Anxiety and Depression Scale – Anxiety
HAD-D	Hospital Anxiety and Depression Scale – Depression
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare professionals
HES	Hospital episodes statistic dataset
HIT-6	Headache Impact Test 6
HVF	Humphrey visual fields
ICHD-3	International Classification of Headache Disorders 3rd edition
ICP	Intracranial pressure
IIH	Idiopathic Intracranial Hypertension
IIHWOP	IIH without papilloedema
IIHWT	Idiopathic Intracranial Hypertension Weight Trial
ICD-10	International Classification of Disease, 10th revision
IHS	International Headache Society
JLA	James Lind Alliance
LogMAR	Logarithm of the minimum angle of resolution
LP	Lumbar puncture
LPOP	Lumbar puncture opening pressure
MD	Mean deviation
MR	Magnetic Resonance
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
OCT	Optical Coherence Tomography
OPCS-4	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision)
PMD	Perimetric mean deviation
PROMs	Patient reported outcome measures
PSP	Priority Setting Partnership
QEHB	Queen Elizabeth Hospitals Birmingham
RCOphth	Royal College of Ophthalmologists
RNFL	Retinal nerve fibre layer
SD	Standard deviation
SIG	Specialist interest group
SITA	Swedish Interactive Testing Algorithm
UHB	University Hospitals Birmingham
UK	United Kingdom

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Chapter 1

1.1 Overview

Idiopathic intracranial hypertension (IIH) is a condition of raised intracranial pressure (ICP) without a known underlying cause.[1] The clinical syndrome's nomenclature has changed over time with initial terms such as serous meningitis, pseudotumour cerebri and benign intracranial hypertension superseded to reflect the advancing knowledge of the condition.[2] As the disease can cause significant morbidity with chronic headaches and visual loss, the term "benign" has been phased out.[3,4] Idiopathic intracranial hypertension is currently defined by a set of diagnostic criteria where a definite diagnosis is conferred when there is: papilloedema; a normal neurological examination except for cranial nerve abnormalities; normal brain parenchyma without hydrocephalus, mass or structural lesion and no abnormal meningeal enhancement or venous sinus thrombosis on neuroimaging that includes venography; a raised lumbar puncture (LP) opening pressure (LPOP) ≥25 cm of cerebrospinal fluid (CSF) performed in the lateral decubitus position; and normal CSF composition.[5]

It has been established that the condition is more common in women and that the main risk factors identified for developing IIH is weight gain and living with obesity.[6,7] As the developed worldwide obesity epidemic has evolved,[8] people with IIH accessing hospital services is becoming much more common. However, the majority of women living with obesity do not develop IIH. People living with active IIH and obesity have been found to have with insulin resistance, hyperleptinaemia, and adverse cardiovascular outcomes. It has been observed that their adipose tissue is predominantly located in the truncal region and, on detailed laboratory analysis, the adipose cells are primed for weight gain. People living with IIH exhibit androgen excess, altered glucocorticoid regulation and changes in pro-

inflammatory cytokines. There are distinct alterations in metabolic pathways found in serum, urine and CSF, that resolve following disease remission.[1]

In 2015 a Cochrane review stated that there was little evidence to guide treatment in IIH.[9] The aim of this thesis was to demonstrate that empowering patients and physicians to advance patient care through a clinical research programme would be a successful method to change clinical practice and reduce patient morbidity.

1.2 Epidemiology

The historic annual incidence of IIH had been reported at approximately 1 per 100,000 in the general population between 1990 and 2001; this increased to 2.4 per 100 000 in the following decade.[10] It was observed that women of childbearing years living with obesity were most commonly affected. Only 10% of IIH cases have been found to be male and only 5% are older than 50 years.[10] Specifically in the United Kingdom (UK), a study found that between 2007 and 2008 the incidence in Sheffield was 1.56/100,000/year in the general population and 2.86/100,000/year for women. This increased in the population of obese women to 11.9/100,000/year. Importantly for health care services, the prevalence in obese women was 85.7/100,000.[11] Further to this study, the Scottish Ophthalmic Surveillance Unit observed an incidence of 37.9/100,000 in obese females aged between 15-44 years between November 2016 and October 2017.[12] The documented increasing incidence and prevalence suggested that IIH was no longer a rare disease.

It is important to establish the contemporary incidence and prevalence, and to identify any changing patterns to ensure feasibility for clinical trials in England and target area with the highest disease burden. An observational analysis of the English Hospitals Episode Statistics (HES) was undertaken to determine the incidence, prevalence, and the socio-economic and racial variation within NHS England of IIH.[13] The HES dataset is a source of large data to

inform the English health economy about disease burden and guide the agenda for future pathways and care. It is an administrative data set detailing inpatient admissions in England across all National Health Service (NHS) and private medical providers. It was expected that persons with IIH would present to hospital services and hence the HES was a database to enable an estimate of the IIH population. Codes on medical classifications (International Classification of Disease, 10th revision) and procedural classifications (Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision [OPCS-4]) were curated to include all IIH admissions over a 14 year period between 31st December 2016 and 1st January 2002. Patient demographics at the time of admission including sex, ethnicity, geographical region and the 2010 Index of Multiple Deprivation (to reflect socio-economic deprivation) were extracted. As the HES dataset did not include all clinical measures, including body mass index (BMI), the national rates of obesity per region were correlated with the incidence of IIH across the same geographical region. Documented sight loss, surgical interventions and obstetric history were also recorded.[13]

The results indicated that there were 23,182 individuals diagnosed with IIH within the study period in English hospitals. The incidence of IIH in the English general population grew from 2.26 per 100,000 in 2002 to 4.69 per 100,000 in 2016. As expected, the incidence was higher in females with 3.53 per 100,000 women in 2002, rising to 7.69 per 100,000 women in 2016. The highest likelihood of being diagnosed with IIH was found in people between the ages of 20-29 years; and being of a white ethnicity represented 75% of the included people.[13]

1.3 Challenges identified for the policy makers, physicians, and patients

The 2018 IIH HES study noted key challenges for UK ophthalmologists, neurologists and policy makers due to the increasing incidence of IIH and increasing repeat hospital

admissions. The inpatient workload was considerable with 47,982 admissions, which represented a 440% rise over the study period. Many individuals had repeated admissions. This could indicate that treatments were unsuccessful at alleviating symptoms, or indeed, at putting the disease into remission. The majority of IIH cases were recorded in areas of highest social deprivation, which included high incidences and prevalences in the East of England and in the West Midlands.[13] This finding was also confirmed in the Scottish Ophthalmic Surveillance Unit study, who considered that social deprivation was likely linked to living with obesity, rather than it being an independent risk factor.[12] Living in social deprivation is a well-known barrier to accessing timely care and within the appropriate environment.[14]

For health care planning the study observed estimated hospital costs rising over the study period from £9.2 to £50 million per annum. A health economic projection was made that an estimate of £462 million per annum would be required to care for people living with IIH in England by 2030 if no changes occurred to the pathway and treatment of people living with IIH.[13]

While a clear limitation of an administrative database is the lack of clinical information, the HES did code for surgical procedures and visual loss. Surgery specific to IIH, such as neurosurgical shunting, optic nerve sheath fenestration and intracranial venous sinus stenting was uncommon in the population, at 8%. There was a low, but present, documentation of visual loss at 2%. In particular, coding of visual loss was not defined and would have been documented at the time of likely diagnosis in the majority, which probably could have introduced bias.[13] A British Ophthalmological Surveillance Unit survey found that between 1-2% of new cases of IIH would become blind within one year.[15] The rate of documented visual loss in both the HES data and the British Ophthalmological Surveillance

Unit study were remarkably similar. However, there could still be established visual loss in people with IIH that confers morbidity without meeting the criteria for obtaining a certificate of visual impairment. Certainly, historical hospital based studies had indicated a much higher rate of visual loss.[3,16,17,18]

Most of the focus for research was in documenting vision and headache outcomes, and as experience within the clinical setting was intensifying, it was clear that maternal health was a concern for patients and obstetric and gynaecology professionals. Within the HES study there was a clear signal of adverse obstetric histories for women with IIH as compared to the general population, with rates of elective caesarean section being significantly higher in people with IIH as compared to the general population, which had not been previously noted. However, it was not possible confirm if this was related to living with obesity or living with IIH, as there was an absence of clinical parameters being held within HES.[13] Further observational studies would be required to corroborate this finding, and to determine causality.

1.4 Harmonising clinical practice for better patient care

Clinical uncertainty in a diagnosis of IIH had been previously demonstrated, particularly by one study that documented a rate of 40% misdiagnosis in a tertiary referral IIH clinic.[19] The management of the disease was also uncertain as the 2015 Cochrane review stated that there was lack of evidence to guide pharmacological treatment in IIH.[9] This, coupled with the rising incidence, prevalence and hospitals admissions for people living with IIH as evidenced by the HES data evaluation, was acknowledged by clinicians across the UK who called for guidance in managing the disease. The Association of British Neurologists (ABN) therefore commissioned the first IIH consensus guidelines with the aim of capturing

interdisciplinary expertise to make recommendations for the investigation of papilloedema and management of IIH, and to identify gaps in the literature.[20]

An initial UK survey to determine preferences in clinical practice in IIH was electronically emailed to large groups of physicians and surgeons who were likely to investigate and manage IIH regularly. Between September 2015 and October 2017 a specialist interest group (SIG) was convened to discuss the background literature and the UK healthcare preferences. The SIG included representation from neurology, ophthalmology, neuro-ophthalmology, neurosurgery, neuro-radiology, nursing, primary care, the IIHUK charity and people with lived experience of IIH. Critical questions to be answered regarding the investigation and management were constructed and agreed upon.[20]

The SIG established diagnostic principles for the investigation of papilloedema. These included: finding any underlying treatable cause in a timely manner; protecting vision and ensuring timely re-examination when vision was found to be at risk; and enabling onward care of the patient to the most appropriate experienced clinician. Uncertainties were documented to be transparent to readers where there was not a high level of evidence, and to encourage researchers to consider areas of unmet need.[20]

When considering the management of IIH the SIG recognised there was a spectrum of the disease ranging from mild to severe, and for the majority of patients the visual prognosis was generally good. They stated that currently weight loss was the only disease modifying therapy for people living with IIH. However, many unknowns existed, such as the amount of weight loss required to put the disease into remission and what weight loss method would be the most sustainable. They recommended that the management of IIH should focus on treatment of the underlying disease, protection of vision and reduction of headache morbidity. An international expert panel was invited to peer review the consensus

statements, to ensure that regional bias had not occurred. Likewise, the document was passed for independent review by the Royal College of Ophthalmologists (RCOphth), the ABN, the Society of British Neurological Surgeons, the British Association for the Study of Headache and to the patient charity IIHUK. Following revision the consensus document was submitted to the Journal of Neurology, Neurosurgery and Psychiatry for further independent peer review.[20]

An aide memoir was developed to broaden the dissemination and subsequent adoption of the consensus guidelines.[21] This infographic representation highlighted key points of interest from the guidelines. Initially, consideration should be given to exclude pseudopapilloedema, a common cause of misdiagnosis.[19] Papilloedema is a medical priority, as it can be caused by an intracranial mass such as a tumour, haemorrhage, or thrombosis and can cause significant morbidity and devastating visual loss. It was critical that the attending doctor understood the importance of assessing visual function. Visual field testing by confrontation is an insensitive test and formal visual fields, preferably automated perimetry, should be sought at the earliest opportunity. Additionally, regular visual field monitoring to detect deterioration is important, as there are limited other clinical biomarkers that can determine the urgency of treatment. A step-wise investigational pathway was recommended. Arterial blood pressure should be measured in all people with bilateral optic disc swelling, as hypertensive emergencies, such as malignant hypertension, are known to cause bilateral optic disc swelling. If malignant hypertension is found, no further investigation for raised ICP is generally required, although brain imaging is often performed.[20,21]

Neuroimaging with cerebral venography is an essential part of the work-up of someone with suspected papilloedema to exclude a venous sinus thrombosis. Imaging should be

performed, where possible, within 24 hours of recognition of the papilloedema. The choice of modality: magnetic resonance (MR) imaging (MRI) versus computerised tomography (CT), would be determined by local access.[20,21] There are key orbital and intracranial neuroimaging features found in people with raised ICP, however these features are also found in normal subjects and within the normal ageing population.[22,23] These signs may not reverse on normalisation of the ICP, and their incidental discovery does not mean that the ICP is currently elevated. Any single neuroimaging feature should not be used in isolation to diagnose raised ICP.[24]

It is commonly accepted that the LPOP reading is abnormal if it exceeds 25 cmCSF in adults and 28 cmCSF in children.[5] In a subsequent large population study the 95% reference interval was found to be between 82 and 242 mmCSF,[25] and repeated LPs demonstrated that LPOP can vary considerably among individuals. This study found that increasing age was associated with a lower LPOP and increasing BMI was associated with a higher LPOP. In those that had a repeat LP at 2.5 years there was a high coefficient of repeatability.[26] The SIG consensus was that there was a "grey zone" of what a cut off should be to diagnose IIH and that between 25cm and 30cmCSF may not be truly pathological, due to the variability in measurements.[21] The LP procedural technique can impact on the reading. Multiple LP attempts which puncture the dura may falsely lower the pressure while abdominal compression from the legs or Valsalva manoeuvres (breath-holding or crying) can falsely elevate the pressure.[20] The CSF should be sent for microscopy (red and white cells), and measurement of glucose and protein levels to help facilitate exclusion of rarer secondary causes. A full blood count should be taken to detect anaemia, as globally, iron deficiency anaemia is prevalent in this patient population, and is treatable. A full medication history is

important, as drug induced intracranial hypertension is typically in response to a temporal relationship with starting or stopping an inciting medication.[20,21]

The principles of management were set out so as to protect vision, manage the underlying condition through weight loss and to reduce headache morbidity. Those identified as having a fulminant course on diagnosis or who demonstrated precipitous visual decline would likely need emergent surgical treatment, preferably with a ventriculoperitoneal shunt, as agreed by the SIG. If this was not readily available then a temporary lumbar drain should be considered. All patients living with obesity and diagnosed with IIH should have a sensitive discussion regarding the evidence for weight loss in inducing disease remission.[20]

The last key area highlighted in the infographic was management of acute exacerbations of headache in a person with IIH; this was included to reduce the unnecessary neuroimaging in those who present with an acute exacerbation of headache.[21] Neuroimaging should be reserved for those who present with red flag symptoms, signs of infection, or papilloedema with precipitous visual decline.[21] The IIH consensus guidelines acknowledged that there were many areas of IIH management that did not have a high quality evidence base. Research into IIH was infrequent due to the previous rarity of disease and a likely lack of understanding of the underlying pathology.[20]

1.5 Empowering patients and physicians to define a research agenda

Raising the profile of the disease and understanding where funding and research should be directed was a priority for IIHUK, the leading UK charity for people living with IIH or caring for people with IIH. They understood that the James Lind Alliance (JLA), a UK National Institute for Health Research-supported initiative, would enable both patients and healthcare professionals (HCP) to work together transparently to agree on the most important uncertainties to inform the research agenda. The IIH priority setting partnership

(PSP) four step process, as set out by the JLA, included an independent information specialist to oversee and guide the process. A broad reach of organisations became partners of the IIH PSP: the ABN; the British Association for the Study of Headache; the British and Irish Orthoptic Society; Fight for Sight; The RCOphth; The Society of British Neurological Surgeons CSF group; Shine; the Neurological Alliance and the United Kingdom Neuro-Ophthalmology Special Interest Group.[27]

The results of the first survey were refined to 'uncertainties 'or 'out of scope 'using the UK Clinical Research Collaboration Health Research Classification System. The interim survey recorded 512 respondents prioritising 48 areas for research. The final long list of 26 priorities were taken to a workshop held at the RCOphth premises in London on 27th April 2018. The top 10 priorities were decided through a series of structured workshops, as defined by the JLA methodology.[27]

Both the JLA IIH PSP and the IIH consensus guidelines detailed a number of uncertainties regarding weight management strategies for people living with IIH, the understanding of headache mechanisms and the best way to monitor visual function.

1.6 Demonstrating weight management as a priority for people living with IIH

It had been established that IIH occurred predominantly in women who are overweight or obese.[6] The population risk of developing IIH increases exponentially in those with a BMI ≥30 kg/m^2.[28] An individual's weight threshold to develop IIH is not clear, and body weight is not a reliable indicator of visceral adiposity. The evidence suggested that weight gain of between 5% to 15% increased the risk of developing IIH.[6] In addition, those people with a BMI under 30 kg/m^2 (non-obese) who gained a moderate amount of weight, were demonstrated to be more likely to develop IIH compared to people with similar BMI whose weight was stable.[6]

Weight loss was first demonstrated to be therapeutic in IIH by Newborg.[29] A low-calorie rice diet with fluid (750–1250 mL/day) and sodium (<100 mg/day) restriction was utilised in a prospective case series of nine IIH patients. The weight loss, between 13–38%, was documented to be associated with improvement in IIH symptoms. These findings were supported by other retrospective case series.[30,31]

The prospective weight loss study, that took place in Birmingham, UK, used a lifestyle intervention of a very low-calorie diet in combination with behavioural therapy, with physical exercise encouraged to induce weight loss of approximately 15%. The women who took part in the study demonstrated a significantly lowered ICP following the weight loss. They also had clinical improvements in their papilloedema and visual field measurements. Headache frequency and severity was halved with a parallel reduction in oral analgesic usage.[32] Weight loss specifically from the truncal region induced remission and, indeed the truncal fat mass correlated with ICP, as measured by LP.[33] While this study proved prospectively that weight loss in IIH helped induce remission, anecdotally these women relapsed with weight gain.

The weight management literature has established that sustained weight loss is difficult to achieve with lifestyle interventions alone as, on average, patients regain one-third to one-half of the weight that was lost at 12 months, and return to their original weight within 5 years.[34] For people with IIH, weight gain has been documented to lead to recurrence of their disease, risking recurrence of papilloedema and damage to the optic nerves.[35] Therefore, a priority for research was to determine sustainable method for weight loss in people living with IIH.

1.6.1 A randomised control trial evaluating weight loss methods in IIH

The aim for the IIH Weight Trial (IIHWT) was to determine whether bariatric surgery or a community dietary programme would provide a more sustainable weight loss method for those with active IIH, in whom previous weight loss methods had been unsuccessful.[36] This UK multicentre, randomised controlled, parallel-arm clinical trial included women with a BMI ≥ 35kg/m^2. This level of BMI chosen for the inclusion criteria mirrored the inclusion criteria for people living with obesity who could be referred to an NHS bariatric surgery programme and in whom there was an established obesity related comorbidity such as cardiovascular disease, hypertension, non-alcoholic fatty liver disease, obstructive sleep apnoea, or type 2 diabetes mellitus. The primary outcome of the study was ICP as measured by LPOP at 12 months. Secondary aims were to evaluate the durability of the intervention, clinical effectiveness, cost-effectiveness, clinical outcomes of headache and vision and, finally patient-centred quality of life outcomes.[36]

Participants randomised to the bariatric surgery arm were referred to the local NHS bariatric surgical pathway and, if judged suitable according to the bariatric surgery clinic's screening processes, would have the option to undergo laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy. The decision as to which surgery type was to be made between the surgeon and participant based on the participant's health circumstances and preference. Participants randomised to the community weight loss intervention (CWI) programme arm were provided with Weight Watcher^{TM} vouchers that exempted them from paying for 52 consecutive and specified weeks of their local Weight Watchers^{TM} meetings. The vouchers included the Weight Watchers^{TM} online and mobile telephone applications. The participant attendance at the groups was monitored through self-reporting.

Ethical approvals was confirmed through the National Research Ethics Committee West Midlands (14/WM/0011) and the trial was registered with the ISRCTN registry (ISRCTN40152829 https://doi.org/10.1186/ISRCTN40152829) and at ClinicalTrials.gov (identifier: NCT02124486). All primary analyses were evaluated by intention-to-treat.

A per protocol analysis was also performed for LPOP and weight change as part of a planned secondary analysis. The per protocol analysis population was defined as those participants in the bariatric arm that had undergone surgery within 12 months of randomisation and the CWI arm where participants did not have bariatric surgery by 12 months. The first patient was recruited on the 25th July 2014.[36]

Among the 66 women randomised, 64 remained in the IIHWT at 12 months, with 54 (82%) completing the primary outcome of LPOP. Intracranial pressure, as measured by LP, was significantly lower in the bariatric surgery arm at 12 months (adjusted mean difference -6.00cmCSF, 95% confidence intervals [CI], -9.5 to -2.4; $p = 0.001$) and at 24 months (adjusted mean difference -8.2cmCSF, 95% CI -12.2 to -4.2; $p < 0.001$). The degree of weight loss was significantly associated with the reduction in intracranial pressure ($R^2 = 0.4734$, $p \leq 0.0001$). Weight loss of 13.3kg (standard deviation [SD] 1.76) was associated with disease remission (LPOP < 25cmCSF). The interventions were demonstrated to be safe in this population with 24 serious adverse events reported over the two years, of which 18 were unrelated to the intervention.[37]

The IIHWT observed significant improvements in health related quality of life indices. The physical component score, energy and fatigue physical functioning, and general health had improvements following bariatric surgery, as compared to the weight watcher arm. At 24 months, there were significant differences in the quality of life outcome measures, supporting the use of bariatric surgery for the improvement of physical functioning and

general health.[37] There were no improvements found in mental component scores, which is consistent with the findings of clinical trials that evaluated bariatric surgery not focused on people living with IIH.[38]

The main limitation of the IIHWT was that the secondary outcomes of vision and headache did not show any difference between the two trial arms. To achieve a difference between the two arms for visual outcomes would have required an approximately five-fold increase in the number of participants.[37]

With the rising costs of healthcare documented by the IIH HES data set,[13] a clear question was whether bariatric surgery was cost effective. Over a 20-year time horizon, the economic modelling found that bariatric surgery led to cost savings of £49,500 over CWI. It also generated an additional 1.16 quality-adjusted life years in comparison to CWI.[39,40]

In the UK, a significant barrier for access to a hospital based weight management programme was that other obesity related co-morbidities, such as type 2 diabetes mellitus or hypertension, were not a typical clinical feature for people living with IIH. Hence, unless their BMI was ≥ 50kg/m^2 they would not be eligible for Tier 3 weight management services that had been demonstrated in the IIHWT to provide disease remission for up to 2 years.

1.6.2 Amount of weight loss required to maintain disease remission

The long-standing clinical question identified by the IIH top ten priorities in the JLA PSP was how much weight was required to be lost to put IIH into remission, with evidence previously suggesting between 3-15% of the diagnosis body weight.[6,32,35] A sub-study of the IIHWT aimed to evaluate the amount of weight loss required to reduce ICP to below the diagnostic level and to explore the impact of the different bariatric surgery approaches. In this planned per protocol analysis of the IIHWT it was found that the greater the weight loss the

greater the reduction in ICP was observed. Twenty four percent weight loss was associated with a LPOP < 25cmCSF.[41]

Within the top ten JLA PSP priorities for IIH it was defined that research to determine if the starting BMI of the patient had an effect.[27] The IIHWT found that those with a higher baseline body weight needed to lose more weight to meaningfully reduce ICP. The magnitude of weight loss demonstrated was unlikely to be achieved without bariatric surgery. This study concluded that referral to a bariatric surgery programme for those with active IIH may be appropriate to reduce the duration of IIH and potential for poor IIH outcomes.[41]

The IIH top ten priorities in the JLA PSP detailed investigation for evidence on what was the best acceptable method to reduce body weight.[27] An analysis of the underlying type of surgery was therefore performed. while the numbers were low in each category, the Roux-en-Y gastric bypass performed the best in terms of reduction of ICP and weight loss. At two weeks following surgery, those who underwent Roux-en-Y bypass had a 50% greater reduction in ICP compared to a gastric sleeve procedure. Subsequent evaluation of the meal stimulation studies undertaken during the IIHWT suggested that this likely occurred by enhanced glucagon-like peptide-1 (GLP-1) secretion in the Roux-en-Y bypass group.[42] It has previously been established that different types of bariatric surgery have variable effects on GLP-1 secretion. Roux-en-Y, which bypasses food to the mid/distal jejunum, exposes L-cells to nutrients, which causes a rise in GLP-1, oxyntomodulin and peptide YY being secreted.[43]

1.7 Discovery of headache mechanisms in IIH

Headache is the most common symptom reported in people with raised ICP.[1] The headache may be a new feature, or it may be a worsening of an existing headache. The headache may vary considerably in terms of frequency, duration, and pain intensity and does not

accurately reflect the ICP or the impact on the visual function.[4] At presentation, the headache phenotype may be worse in the mornings, on lying down, on bending down, and with Valsalva manoeuvres.[44] The challenge is that these features are not exclusive to a raised ICP headache as one third of people living with migraine also have reported exacerbation of headache with coughing and nearly half have exacerbation while bending. As it progresses, the headache may be a daily occurrence, which is diffuse and or constant. It may be pulsating and throbbing, and have associated features of photophobia, phonophobia, nausea, vomiting, and worsening on physical activity.[44] A raised ICP headache phenotype therefore mimics primary headache disorders, such as episodic migraine, chronic migraine and tension-type headache.[4]

Headache mechanisms were highly prioritised, by being cited as the second priority by the IIH JLA PSP.[27] While it would seem plausible that ICP triggers headaches, due to the temporal relationship between disease onset and headache symptoms, research to date had not found an association between headache attributable to IIH and raised ICP.[4] Headaches associated with IIH have been found to be debilitating, and persistent, with many using analgesia for years after a diagnosis.[45] Similar to other randomised control trials,[4] the IIHWT documented the most common headache phenotype as a migraine-like headache.[46] Other phenotypes reported in the IIHWT cohort included IIH headache, medication-overuse headache, and tension-type headache.[46]

The IIHWT found that headache severity correlated with ICP at baseline and change in headache severity and monthly headache days correlated with change in ICP at 12 months. A positive association between ICP and headache was noted in this sub-study using boot strap analysis at 12 and 24 months. This enabled a prediction of both change in headache severity and monthly headache days. Reduction of ICP, as measured by LPOP, was

associated with significant improvements in quality of life using the Short Form-36.[46] Further mechanistic studies using the serum, CSF and urine of IIHWT participants were made. They identified different metabolic pathways related to amino acid, lipid, and acylpyruvate metabolism in the IIHWT participants as compared to control participants. These pathways were associated with clinical measures, such as LPOP, and returned to normal with disease remission[47]

1.8 The challenge of the visual field mean deviation as a trial outcome in IIH

In clinical practice regular assessment of visual function and optic nerve head imaging is necessary to identify those at risk of visual loss.[20] Automated perimetry is routinely employed as it provides sensitivity for assessing changes in the visual field. The Humphrey Visual Field (HVF) mean deviation (MD) has been used commonly as an end point in IIH research.[32, 48] Visual field testing is dependent on the technician and patient performance and results can vary.[49,50] The learning effect can be mitigated by allowing multiple attempts to allow for familiarisation. In the IIH Treatment Trial, up to one in five patients had a performance failure at one data point.[50] Therefore, reliability indices are essential to determine the quality of the test. Further factors exist, such as a high prevalence of functional vision loss being reported in people with IIH, that may impact their visual field performance.[51] Cognitive deficits have been shown to be affected in people with active IIH leading to reductions in reaction time and processing speed that can influence the visual field results.[52,53]

The IIHWT met its primary endpoint, which was change in ICP measured by LPOP at 12 months, however there was no significant improvement seen in the MD, or other visual outcomes, between the two trial arms.[37] To consider future trials, and to calculate a power on which to base numbers for a study, it was important to understand, if MD did not

improve significantly between the two groups, whether another approach be feasible. A pointwise analysis was therefore undertaken to assess if it was a more sensitive indicator of a change in the visual field in IIH patients participating in treatment trials. The results found that those with baseline point sensitivities between 0 and -10dB showed small changes over time and, as expected, were unlikely to demonstrate clinically meaningful change over both 12 and 24 months. Points in the -10 to -25dB category demonstrated change that could be considered clinically meaningful (mean 8.5dB in at least one point in the whole visual field). The challenge was that using data between -10 and -25dB resulted in fewer data points and larger SD for analysis. Although the median number of points worse than -10dB was five, only 43% of all the IIHWT participants had fewer than two points worse than -10dB at baseline. This confirmed that data points worse than -10dB were not representative of the majority of IIH patients in a trial setting and that if a trial was powered on these types of data it would be even less representative of the whole IIH population.[54]

1.9 Informing others of lessons learnt in controlled clinical trials in IIH

The strength of this thesis is that numerous research methods have been employed such as data driven observation, literature review, convening of expert patient and health care opinions, and performing a randomised control trial to achieve solutions to unknowns in IIH.[13,20,27,37] The lessons learnt about the condition and clinical trial delivery were distilled into the commissioned International Headache Society (IHS) Guidelines for Controlled Clinical Trials in IIH.[55] This research guideline aimed to establish recommendations for designing state-of-the-art controlled clinical trials for IIH to advance treatment, inform regulatory decision making and to enable meta-analysis.[55]

A summary of the IIH trials preformed to date and documented primary and secondary outcomes was made. An IIH trial guideline subcommittee, which consisted of

ophthalmologists, neurologists, trialists and patients met to discuss the literature and decide the outcomes that were deemed important. The format followed the IHS guideline methodology. It was sent for comment to various stakeholders that included pharmaceutical and devices manufacturers. It was posted for a specified time on the IHS website and IHS members were then invited to comment. Following all revisions, it was sent for final approval to the IHS Board of Trustees. While there are inherent limitations on consensus-type guideline, this document contained many considerations that may not initially be obvious to those embarking on a clinical trial in IIH for the first time.[55]

1.10 Limitations

The limitations of each publication included in this thesis are discussed in the individual papers.[13,20,21,27,37,41,46,54,55] The consensus guidelines, the IIH JLA PSP and the IIH IHS guidelines for clinical trials are likely subject to bias as they are based on informal group decision making.[20,27,55] Individuals running these processes may have dominated discussions and created an imbalance of opinion. To minimise this balance the JLA PSP process employed a normal group technique of independent generation of questions, grouping of categories, clarification and then ranking of priorities.[27] The IIH JLA PSP research priorities held many similarities to the uncertainties discussed in the IIH Consensus Guidelines.[20,27] A further limitation of inclusion is likely to be, as identified by the HES study,[13] that a significant portion of patients who live with IIH also live with social deprivation. While efforts were made in terms of reducing digital exclusion, more work is required to include hard to reach individuals both in consensus about their care and in randomised control trials.

The limitations specific to the IIHWT was that it had to balance delivery of a specific research question evaluating two weight loss methods over financial and participant

feasibility. The major drawback for the IIHWT was the lack of corresponding signal in the important clinical symptoms of IIH, headache and visual function. This has likely impacted on the directed use of bariatric surgery in women with active IIH with a BMI 35kg/m^2.[37]

1.11 Recommendations for clinical practice

Diagnosing, monitoring and treating people with IIH require a combination of skills in assessing the visual function and headache. People with IIH are best monitored by both a neurologist and an ophthalmologist. The IIH consensus guidelines provided a template for clinicians to be able to shape their own practice.[20] When a repeated study of the English HES was performed, it was noted that there was a reduction in surgical procedures for IIH, which may have been as a result of the consensus guidelines.[56]

The IIHWT demonstrated that there was a hierarchy of effect in weight loss methods found to be effective in reducing ICP, with bariatric surgery having the most robust evidence for effective treatment of obesity in a female IIH population with a BMI ≥35kg/m^2.[37] World-wide, not all patients will qualify for bariatric surgery intervention. Following the publication of IIHWT and the cost utility analyses the UK National Institute of Health and Clinical Excellence (NICE) revised their clinical guidelines for obesity. The NICE clinical guidelines for obesity 2023 now include IIH as a significant condition that could be improved by weight loss, alongside the previously recognised conditions that could be improved after weight loss including: cardiovascular disease; hypertension; non-alcoholic fatty liver disease, obstructive sleep apnoea; and type 2 diabetes mellitus. The implication of the inclusion of IIH means that people living with obesity and IIH could be referred to specialist weight management services. The criteria now recommended bariatric surgery as a treatment option for people with a BMI ≥40kg/m^2, or with a BMI of 35-39.9kg/m^2 with a significant

obesity-related comorbidity, such as IIH, only if all non-surgical interventions had been tried first and the person was receiving management in a tier 3 service. For people of South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background referrers can consider using a lower BMI threshold for referral (reduced by 2.5 kg/m^2).[57,58]

1.12 Recommendations future research

Obesity stigma amongst health care professionals and patients has been documented to significantly obstruct progress and is associated with poorer patient outcomes. Education and understanding may help to overcome this significant barrier in the treatment of IIH. A patient-led research project voiced barriers in professional language that have been disseminated.[59]

The adverse obstetric outcomes found in the HES dataset led to a number of analyses of IIH Life, a prospectively held database, a further analysis of the HES evaluating women's health in IIH and studies investigating the association and similarities of polycystic ovarian syndrome.[60,61,62,63] Recommendations were also made for managing women with IIH in pregnancy.[64]

The cumulative knowledge gained over this study of IIH provided the opportunity to deliver an international multidisciplinary research guideline for IIH under the auspices of the IHS.[55] This shared learning opportunity may aide others in the understanding of effective clinical trial outcomes. This has been particularly important as recently two large international multicentre trials have prematurely closed due to lack of recruitment.[65,66]

1.13 Conclusions

The direct impact of this work, from the first IIH guidelines to delivering the successful IIHWT has afforded a change in the obesity national guidelines for people living with obesity and IIH. The evidence presented within this thesis have created the foundations for future work to move therapies from early phase trials to large multicentre trials and ensure clinical delivery. This work has delivered a ranking of research priorities for the UK and international clinical and research guidelines. The randomised control trial IIHWT evaluating bariatric surgery compared to a lifestyle intervention for sustained remission of the disease has changed national guidelines for entry to a bariatric surgery pathway.

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Summary sheet

1 Mollan SP, Aguiar M, Evison F, Frew E, Sinclair AJ. The expanding burden of idiopathic intracranial hypertension. Eye (Lond). 2019;33(3):478-485.

2 Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, Krishnan A, Chavda SV, Ramalingam S, Edwards J, Hemmings K, Williamson M, Burdon MA, Hassan-Smith G, Digre K, Liu GT, Jensen RH, Sinclair AJ. Idiopathic intracranial hypertension: consensus guidelines on management. J Neurol Neurosurg Psychiatry. 2018;89(10):1088-1100.

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Involvement:
I set up the inclusions and exclusion codes for the hospital episode statistic searches, refined the data collection, aided the analysis, wrote the first manuscript, critically revised the manuscript. I further disseminated this work as a platform presentation at the Association of British Neurologists Annual meeting in 2018.

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

ARTICLE

The expanding burden of idiopathic intracranial hypertension

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Abstract

Objective To quantify the hospital burden and health economic impact of idiopathic intracranial hypertension.

Methods Hospital Episode Statistics (HES) national data was extracted between 1st January 2002 and 31st December 2016. All those within England with a diagnosis of idiopathic intracranial hypertension were included. Those with secondary causes of raised intracranial pressure such as tumours, hydrocephalus and cerebral venous sinus thrombosis were excluded.

Results A total of 23,182 new IIH cases were diagnosed. Fifty-two percent resided in the most socially deprived areas (quintiles 1 and 2). Incidence rose between 2002 and 2016 from 2.3 to 4.7 per 100,000 in the general population. Peak incidence occurred in females aged 25 (15.2 per 100,000). 91.6% were treated medically, 7.6% had a cerebrospinal fluid diversion procedure, 0.7% underwent bariatric surgery and 0.1% had optic nerve sheath fenestration. Elective caesarean sections rates were significantly higher in IIH (16%) compared to the general population (9%), $p < 0.005$. Admission rates rose by 442% between 2002 and 2014, with 38% having repeated admissions in the year following diagnosis. Duration of hospital admission was 2.7 days (8.8 days for those having CSF diversion procedures). Costs rose from £9.2 to £50 million per annum over the study period with costs forecasts of £462 million per annum by 2030.

Conclusions IIH incidence is rising (by greater than 100% over the study), highest in areas of social deprivation and mirroring obesity trends. Re-admissions rates are high and growing yearly. The escalating population and financial burden of IIH has wide reaching implications for the health care system.

Introduction

In light of the growing obesity epidemic, re-evaluation of trends in idiopathic intracranial hypertension (IIH) are needed. This would inform the agenda to standarise care pathways, improve quality of care provision and drive developments in novel therapeutic options to reduce the burden of this expanding disease.

IIH is a condition of unknown aetiology which occurs predominantly in obese women [1, 2]. There are currently few treatment options for IIH [3], management is typically medical, with those experiencing progressive visual loss undergoing surgical procedures [4]. Currently weight loss is the only disease modifiable therapy [5].

IIH was considered a rare condition. Previous annual incidence was reported at approximately 0.5–2 in 100,000 in the general population [6–12]. Prevalence data is sparse for the United Kingdom (UK) but a retrospective case review has reported prevalence of 10.9 per 100,000 for the general population in Sheffield, UK [6]. It has been widely speculated that the incidence of IIH is increasing in line with the world-wide epidemic of obesity [2, 10, 12].

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Despite the relative rarity of IIH the multidisciplinary manifestations of the condition leads these patients to access hospital care though a large number of hospital specialties. In the UK suspected patients attend accident and emergency departments, are admitted to hospital or have procedures on ambulatory day care units. The scale of emergency room attendances, hospital admissions and day case care in the England has not been previously reported. Previous data from the United States has highlighted the economic burden of IIH [13, 14].

This observational study aimed to use Hospital Episode Statistics (HES) dataset to quantify incidence trends over time within England. We sought to define incidence by geographical distribution and socio-economic deprivation as well as determine the annual admission rates, management strategy (medical vs. surgical) as well as obstetric outcomes. The secondary aims were to conduct a health economic evaluation to establish the financial impact.

Methods

Study design and setting

This study was conducted through use of registered national data sets, and included all patients with IIH admitted for hospital care in England between 1st January 2002 and 31st December 2016. Data were obtained from the HES, an administrative dataset covering all NHS Trusts in England, which processes over 125 million admitted patient, outpatient and accident and emergency records each year; generating a log of each clinical episode taking place in NHS hospitals or NHS commissioned activity in the independent sector (private care). Admitted patient care episodes are defined as emergency room attendances, ambulatory care attendances (for example for lumbar puncture) and inpatient care [15].

Each record is anonymised and comprises specific demographic details of the admitted patient including age group, gender, ethnicity and geographical information such as where patients are treated and the area where they live (it is worth noting that body mass index data is not recorded). Data was checked for duplicate patient identifiers to ensure there was no double counting of entries. University Hospitals Birmingham NHS Foundation Trust holds a Data Re-Use Agreement for the interrogation of the HES. The research involved non-identifiable information, previously collected in the course of patient care and available for public use.

To access information pertaining to all IIH admissions, validated International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes and procedural classifications from the Office of Population, Censuses and Surveys Classification of Interventions and Procedures, 4th revision (OPCS-4) codes were used (supplementary file 1).

Exclusion criteria were applied to help refine the data and ensure against miscoding of secondary causes of raised intracranial pressure such as tumours, hydrocephalus and cerebral venous sinus thrombosis (supplementary file 1). Due to the very high number of admitted patient care and comorbidities, we exclude those with a history of dialysis, as the high admission rates would have potentially biased the results.

Data collection

Patient demographics at the time of admitted patient care episodes were recorded and included gender; ethnicity; geographical regional location, as classed by the Government Office Region (GOR); and social deprivation indices based on the English index of multiple deprivation (IMD) 2010. The IMD is the official measure of relative deprivation (for neighbourhoods) in England and has been used frequently as a measure of relative deprivation to guide resource allocation and provision of services in the United Kingdom. Deprivation in this context refers to the relative disadvantage an individual experience living in a certain area. The IMD is based on 38 routinely collected indicators, aggregated into seven weighted domains to represent different dimensions of deprivation, namely income, employment, health and disability, education and skills, barriers to housing and services, crime and environment.

The IMD uses an area-based model at a low geography (average of 1500 people). Ranking the areas from 1 (most deprived area) to 32,844 (least deprived area) and quintiles are calculated dividing the ranking into five equal groups [16].

World Health Organisation (WHO) obesity data, only available up to 2014, was used to estimate UK obesity trends. Obesity is classed as a body mass index (BMI) ≥ 30 and is age-standardized in18 years+ by gender in the UK. National rates of obesity from Health survey for England 2015, were used for correlation of obesity rates per deprivation quintiles [17].

Visual complications and related surgical treatments, including cerebrospinal fluid diversion procedures, optic nerve sheath decompression and bariatric surgery, were recorded in this cohort. Cerebral venous stenting was initially scoped, but the multiple codes used to define one procedure varied greatly, and the data here would have been inconsistent and inaccurate. To investigate women's health through pregnancy outcomes, the IIH cohort was matched against HES data from the general population for number of live births and mode of delivery.

Economic model methods

To estimate the direct health care costs of IIH, a patient pathway model was developed based on the HES data presented here, and the Cambridge shunt registry [18]. Only direct health care resources associated with the diagnosis and treatment of IIH were included and no costs relating to the wider economy (such as days lost to work, childcare costs or travel to hospital) were calculated. The cost data applied to the health care resource use was taken from Optom [19], 2015–16 NHS reference costs [20] and the British National Formulary [21] (supplementary file 2).

The pathway model was developed to illustrate each step of the patient pathway for the first year and tree diagrams were constructed (supplementary files 3,4). In addition to those already cited, to predict future costs other sources were utilised [22, 23] (supplementary file 5).

Statistical analysis

The data were initially explored through descriptive analysis of variables using *t* tests for quantitative variables and a χ^2 test for categorical variables to compare different groups. Incidence and obesity data were normally distributed and pearson correlations were utilized. All statistical analyses were conducted using GraphPad Prism™ (version 7.04).

Results

HES identified 26,565 unique patients coded with IIH (ICD10 = G932) between 1/1/2002 and 31/12/2016. To ensure that an unbiased representative population was analysed 3383 were excluded from the analysis (Fig. 1).

The number of individual patients diagnosed with IIH was 23,182 during the study period (Fig. 2). 17.6% (4079/23,182) were male and 82.4% (19103/23,182) were female. The median age at diagnosis was 28 years (range: 21–40 years) (Fig. 2b; supplementary file 6).

With males having a higher median age of 32 years (range 14–50 years) and women a lower median age of 28 years (range: 22–38 years) (Fig. 2b). The majority of the ethnic groups reflected the population of England, with white being the prominent category in IIH (supplementary file 7).

Incidence of IIH

In the general population, the incidence of IIH increased by 108% over the study period; in 2002 it was 2.26 per 100,000 rising to 4.69 per 100,000 in 2016 (Fig. 2a). Overall the peak incidence was seen in females aged 25 years and was 15.2 per 100,000 (Fig. 2b). The incidence in females in 2002 was 3.53 per 100,000 rising to 7.69 per 100,000 with the rates increasing in line with obesity in females ($r = 0.914$, $P < 0.0001$) and also in males (0.9 per 100,000 to 1.6 per 100,000, $r = 0.913$, $p < 0.0001$) (Fig. 2c). This represents a 118% increase in incidence in females.

IIH incidence varied with geographical region across the UK with greater incidence noted in the East of England and the West Midlands (supplementary file 8, Figs. 2e, f). Cases of IIH varied with social deprivation (Fig. 3). Fewer cases are recorded in least deprived areas (deprivation quintile 5, 3080 (13.3%) cases of IIH). Whilst in areas of higher deprivation (deprivation quintiles 1 and 2) the majority of IIH cases were recorded (12,136 cases, 52.3%) (Fig. 3a).

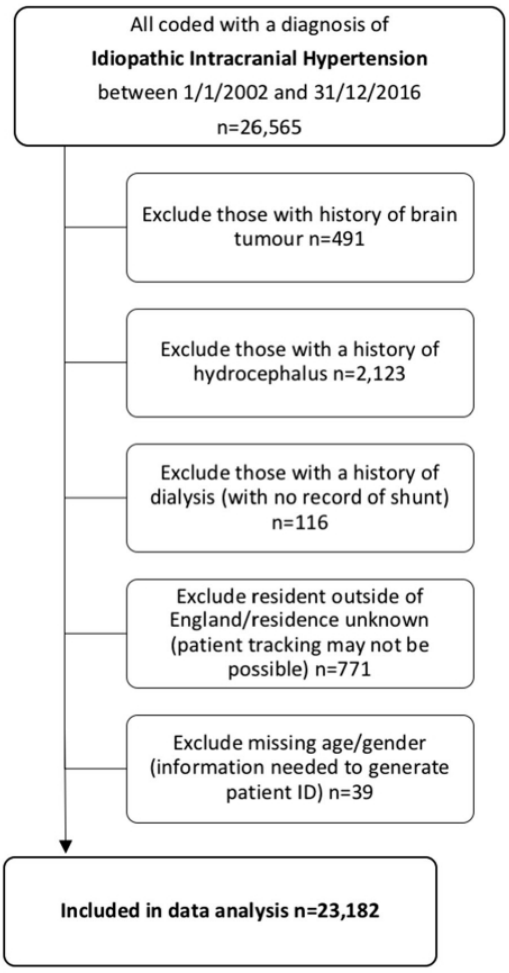

Fig. 1 Consort diagram

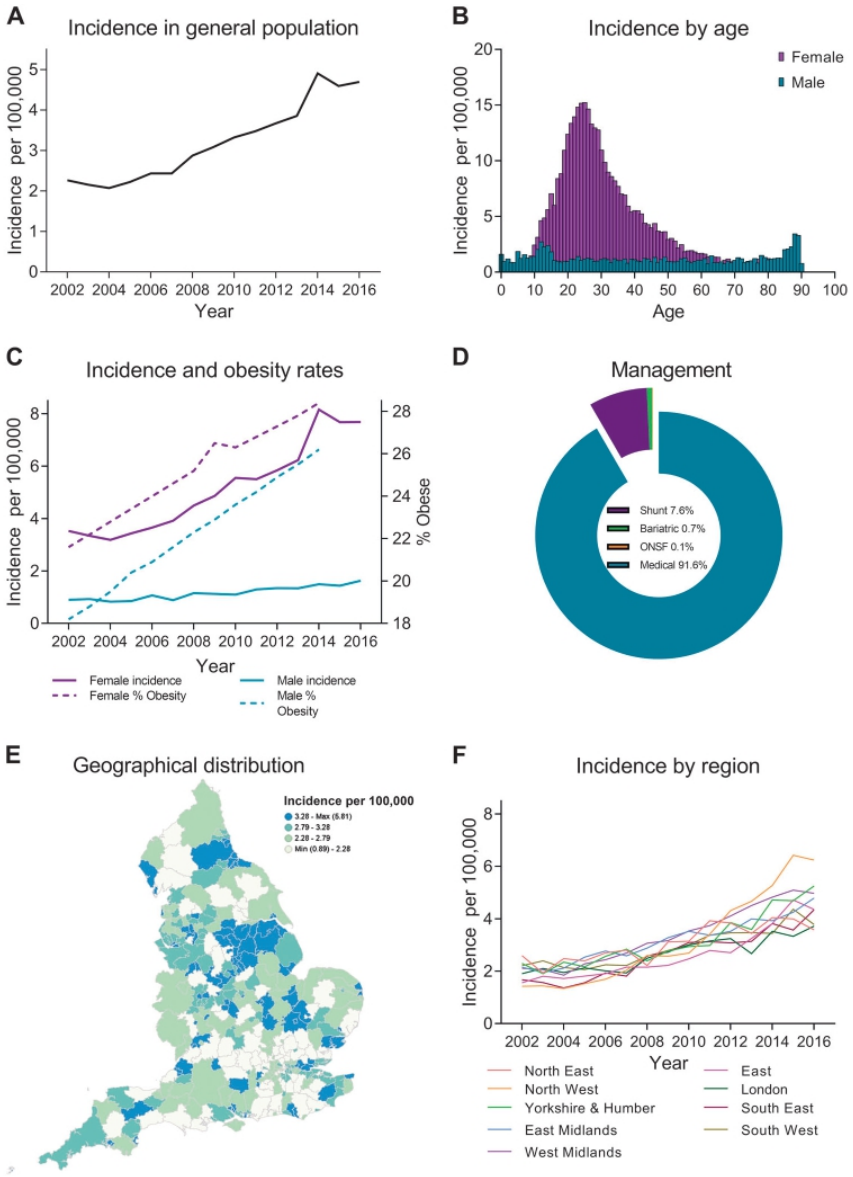

Fig. 2 Composite figure. **a** Incidence in the general population. **b** Incidence by age and gender. **c** Annual incidence in females and males and Obesity rates (% obesity per annum (body mass index ≥ 30), age-standardized in 18 years + by gender in the United Kingdom. From World Health organisation http://apps.who.int/gho/data/node.main.A900A?lang=en Accessed 6 Oct 2017. **d** Management of IIH in the cohort. **e** Geographical distribution of diagnosed cases of IIH in England. **f** Distribution of cases by region per annum

The relationship between IIH and social deprivation varied with gender, with female cases significantly correlating with deprivation $r = 0.89$, $p < 0.001$, but this was not apparent in male cases ($r = 0.37$, $p = 0.539$) (Fig. 3a). BMI is known to differ with deprivation quintiles [17], and here amongst the female IIH population, cases correlated with deprivation quintile BMI ($r = 0.98$, $p = 0.003$), however male gender did not ($r = 0.59$, $p = 0.291$) (Fig. 3a).

Admitted hospital episodes

Between 2002 and 2014 there were 47,982 hospital admitted patient care (emergency room attendances, admitted inpatient episodes and ambulatory care episodes) for IIH (Fig. 3b) for 23,182 patients. Over the study period there was an increase in admitted hospital episodes for IIH by 442% (1315 to 7123 patients admitted per year over the study period). Over half of the cohort had only one

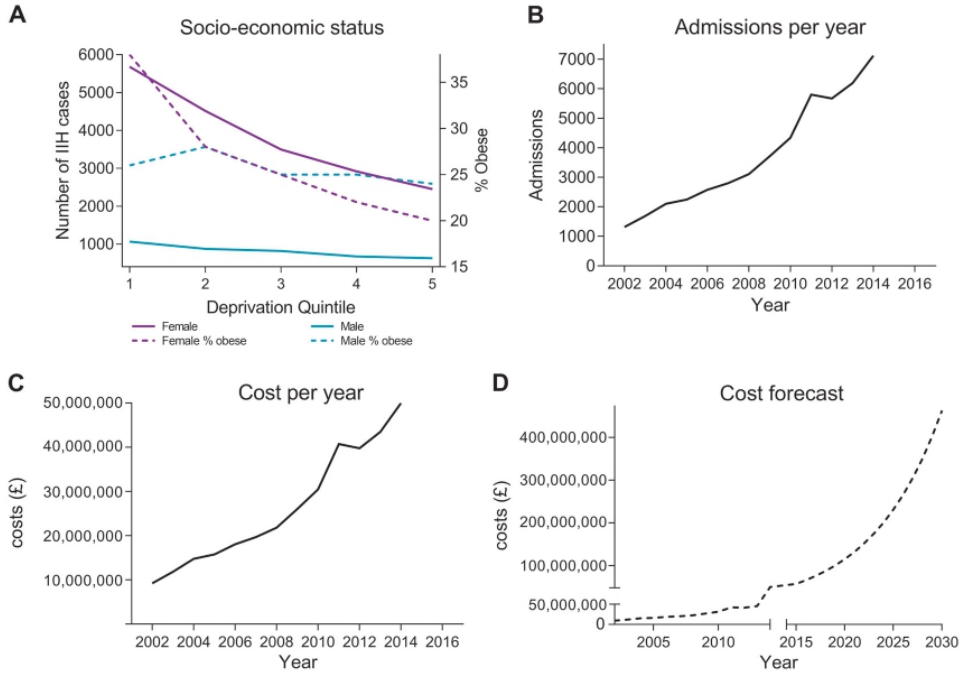

Fig. 3 **a** IIH cases according to gender and socioeconomic status (solid line). % obesity rates (body mass index ≥ 30), age-standardised (aged > 16) by equivalised household income and sex (dotted line), data from Health Survey for England 2016. **b** Annual hospital episodes for IIH. **c** Hospital costs per annum for IIH. **d** Future predicted costs in millions (£) of IIH in England based on current trends

admission episode and no further admitted hospital care in the year following the diagnostic episode coded for IIH. 37.8% of the cohort had repeat hospital admissions in the first year following their diagnosis (supplementary file 9), with 0.9% having 10 or more admitted hospital episodes.

The average length of stay was 2.7 days, for those who had no surgical procedure, and for those who undergo neurosurgical management was 8.8 days. Over the study period, the majority were managed medically (91.6%); 7.64% (1771/23,182) had a shunt procedure; 0.68% (158/23,182) underwent bariatric surgery; and 0.07% (10/23,182) had an optic nerve sheath fenestration (Fig. 2d).

Morbidity

Following diagnosis of IIH, according to HES records, 99 were coded as blind and 349 as visually impaired. Therefore, any type of visual impairment following a diagnosis of IIH is seen in 1.92% (445/23,182) of the cohort (with 0.42% being blind and 1.49% being visually impaired).

Obstetric health

Those women between 16 and 55 years with IIH had similar birth rates to those in the general population of the same age range (supplementary file 10). IIH women were statistically less likely to have a normal delivery compared to age matched women in the general population with 4839 (57.44%) of women with IIH having a normal delivery compared to 3,612,199 (64.09%) in the general population, $p < 0.005$. Women with IIH were significantly more likely to undergo elective ($n = 1328$) and non-elective caesarean sections ($n = 1427$) compared to the general population (elective $n = 514{,}287$; non-elective $n = 960{,}394$), $p < 0.005$.

Economic estimate

IIH was estimated to represent an annual hospital healthcare cost of £7016 per patient. When combined with the IIH population incidence rates, the total cost of IIH hospital care has risen dramatically from £9.2 million in 2002 to £49.9 million in 2014 (Fig. 3c). A prediction of future economic hospital burden was based on the current cost estimation and the expected population trends: if the rising trends of IIH continue then by 2030 it is projected to cost hospitals in England £462.7 million (Fig. 3d).

Discussion

In this observational study of HES data the increase in IIH incidence by 108% is described. Of note the rising

incidence significantly correlates with rising BMI in both genders, which has been previously speculated [4]. The incidence in women is four fold higher than in males (7.7 women vs. 1.6 per 100,000 male), with a peak incidence in women at the age of 25 years (15.2 per 100,000). Adult IIH has not been previously associated with social deprivation and adverse obstetric outcomes. These factors are new signals which reinforce that this disease should not be assumed "benign".

Over half of the cohort was recorded in the lowest two quintiles of the IMD. Deprivation and social determinants are well known to cause a wide range of adverse health effects and are associated with higher morbidity and mortality [24, 25]. Area deprivation, as measured utilizing IMD, is an aggregated marker of social deprivation [25]. It is reliably used and has been associated with poorer clinical outcomes [26] and an increased number of co-morbidities [27, 28]. We have shown that IIH cases are significantly associated with deprivation quintile specific BMI rates (Fig. 3a) and we hypothesise that increased BMI may be a predominant factor in determining the variable in IIH social deprivation.

Over a third of the cohort had multiple hospital admissions (emergency room, inpatient or ambulatory care episodes) within the first year following diagnosis (Table 1); a 442% increase in admissions in the period studied. Deprivation status has been found to strongly influence admission and readmission rates for medical patients [29]. Primary care and unplanned hospital services are accessed more by those in deprived areas than those who are not [30] and those from deprived areas are less likely to visit a secondary care specialist [31]. National consensus guidelines could potentially help to reduce these attendances [32].

A prevalence study [33] reported 1–2% severe visual loss in IIH within the UK. The visual loss rates reported here are 1.92% of this English cohort, with 0.42% being blind and 1.49% with any kind of visual impairment. These rates may be an underestimation due to the differences in the definitions of visual impairment between the coding in HES and national definitions for certificate of visual impairment (supplementary file 1) [34]; and potentially represent underreporting of comorbidities in the HES data. Linkage of the HES and the certificate of visual impairment register was not possible with this anonymized study design.

The major strength of this study is that the analysis covers all IIH patients admitted hospital episodes in English NHS and private hospitals over a 14 year period and is therefore a unique population-wide assessment. Using national data over a long time-period allows for variation across the years. Unlike insurance company data our data is unlikely to be biased due to variation in funding between hospitals, insurance coverage or the patients' ability to pay for care. However, like any database improvements in clinical record keeping and hence coding will improve the accuracy of the data. Likewise, we cannot be sure each of the individuals fulfilled the diagnostic criteria for IIH, and are dependant on the medical staff to make accurate diagnoses [1]. Changes in awareness of the condition and the medical literature, such as publication of revised diagnostic criteria [1], could have inflated the incidence following publication. Within the results there is a portion of patients diagnosed over the age of 65 years (supplementary Table 5), these cases likely represent misdiagnosis of phenotypical IIH, as the natural history of the disease is within the younger age ranges [2, 4].

Obstetric health is important in IIH, as the majority are women of child-bearing age (Fig. 2b). Literature in this area is case based [35]. Although those with IIH have similar parity compared to the general population (supplementary file 10) they were significantly more likely to undergo both elective and non-elective caesarean sections compared to the general population. This may be due to the association of obesity, as higher rates of caesarean section are reported in overweight and obese individuals [36]. Practical guidance in IIH does not suggest opting for caesarean section based solely on the diagnosis of IIH and as the transient elevations in ICP during the second stage of labour are unlikely to impact on the optic nerve function, except in the setting of fulminant IIH [32].

IIH is considered rare, however the rising incidence, hospital episodes and subsequent economic impact are noteworthy with wide reaching implications for health care service provision. The consensus guidelines [32] will start to shape and standardised care pathways and improve the quality of care. Development of novel therapeutic options may help to reduce the burden of this expanding disease.

Summary

What was known before

- Previous annual incidence was reported at approximately 0.5–2 in 100,000 in the general population.
- It has been widely speculated that the incidence of IIH is increasing in line with the world-wide epidemic of obesity.
- No previous studies have determined IIH as a disease predominantly associated with social deprivation.

What this study adds

- In this study of 23,182 IIH patients incidence is rising (4.69 per 100,000 in 2016) and this in line with increasing body mass index rates.

- IIH is more commonly found in those from areas of social deprivation.
- The hospital economic burden has risen from 9.2 million in 2002 to 49.9 million in 2014.

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Statistical analysis Statistical analysis was performed by F. Evison and A. J Sinclair PhD, both University Hospitals Birmingham NHS Foundation Trust.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval University Hospitals Birmingham NHS Foundation Trust holds ethical approval for interrogation of the Hospital Episode Statistic database.

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Supplementary File 1:
Inclusion and exclusion codes used in the search strategy. To access information pertaining to all IIH admissions, validated International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes and procedural classifications from the Office of Population Censuses and Surveys Classification of Interventions and Procedures, 4th revision (OPCS-4) codes were used.

Variable	Inclusion Codes	Exclusion Codes
Idiopathic Intracranial Hypertension	ICD-10-CM code: Benign Intracranial hypertension –G93.2 [Hypertension, idiopathic intracranial; Increased intracranial pressure; Pseudotumor cerebri; Raised intracranial pressure]	ICD-10-CM codes: Hydrocephalus G91; Cerebral venous sinus thrombosis G08; Brain Cancer C70, C71; Hypertensive encephalopathy I67.4
Visual outcomes	ICD-10-CM codes: H540 - Blindness, binocular H541 - Severe visual impairment, binocular H542 - Moderate visual impairment, binocular H544 - Blindness, monocular H545 - Severe visual impairment, monocular H546 - Moderate visual impairment, monocular H547 - Unspecified visual loss. H549 - Unspecified visual impairment (binocular)	ICD-10-CM codes: H53.9 visual disturbance, unspecified H470 - Disorders of optic nerve, not elsewhere classified H543 - Mild or no visual impairment, binocular
Past medical history	ICD-10-CM codes: Depression F32 Diabetes E10-E14	
Surgical history-Bariatric Surgery	OPCS-4 codes: G301 G30.1 Gastroplasty NEC G302 G30.2 Partitioning of stomach NEC G303 G30.3 Partitioning of stomach using band G304 G30.4 Partitioning of stomach using staples	

Variable	Inclusion Codes	Exclusion Codes
Surgical history- Cerebrospinal fluid diversion procedures	OPCS-4 codes: A122 A12.2 Creation of ventriculovascular shunt A123 A12.3 Creation of ventriculopleural shunt A124 A12.4 Creation of ventriculoperitoneal shunt A53 A53 Drainage of spinal canal A534 A53.4 Creation of lumboperitoneal shunt A536 A53.6 Creation of lumbar subcutaneous shunt	
Obstetric History	All deliveries- record of ICD-10-CM codes O80-O84 OPCS-4 codes for all types of delivery of baby (R17-24) including: Elective C-section R17 Other caesarean delivery R18 (in labour/emergency) R21 Forceps Cephalic deliveries R21 Forceps delivery R22 Vacuum delivery R24 Normal delivery R24.9 All normal delivery	The data was restricted to only 1 birth in a 9 month period.

Supplementary file 2:
Summary table of all costs included in the economic model analysis and source material from which the individual costs are derived. The model assumes same cost for first shunting surgeries and revision surgeries. Analysis includes direct costs only, related to secondary care and drug therapy prescribed in hospital.

Variable	Cost (£)	Code	Source
Optician visit	20.00	NA	UK Health Centre. 2016 [1]
Accident and Emergency attendance	138.00	NA	NHS Reference Costs 2015-2016 [2]
CT Head Scan	111.00	RD24Z	NHS Reference Costs 2015-2016 [2]
MRI Scan (head and orbit with intravenous contrast)	166.00	RD05Z	NHS Reference Costs 2015-2016 [2]

Lumbar puncture	664.01	AA55	NHS Reference Costs 2015-2016 [2]
Venography	154.50*	U117 and U119	NHS Reference Costs 2015-2016 [2]
Ophthalmology visit (led by consultant)	94.18	130	NHS Reference Costs 2015-2016 [2]
Neurology (led by consultant)	178.94	400	NHS Reference Costs 2015-2016 [2]
Neurosurgery(led by consultant)	204.31	150	NHS Reference Costs 2015-2016 [2]
Optical Coherence tomography (OCT) scan	52.94	RD40Z	NHS Reference Costs 2015-2016 [2]
Humphrey visual field	Included in Ophthalmology outpatient cost	NA	NHS Reference Costs 2015-2016 [2]
Excess bed day	306.00	NA	NHS Reference Costs 2015-2016 [2]
Acetazolamide (cost per year)	663.20	NA	British National Formulary 2016 [3]
Lumbar Peritoneal Shunt (LPS)	4344.99	HC71Z	NHS Reference Costs 2015-2016 [2]
Ventricular Peritoneal Shunt (VPS)	8770.00	AA52	NHS Reference Costs 2015-2016 [2]

NB All costs are indexed for GBP 2016 prices. * 50% were MRV and 50% CTVs.

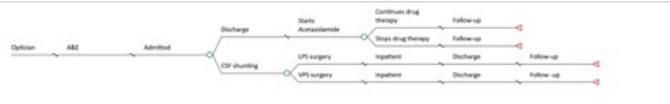
1 UK Health Centre. 2016 (http://www.healthcentre.org.uk/opticians/opticians-opticians-costs.html) Last accessed 19th December, 2017.

2 Department of Health. NHS reference costs 2015 to 2016: National schedule of reference costs. 2016. Last accessed 19th December, 2017.

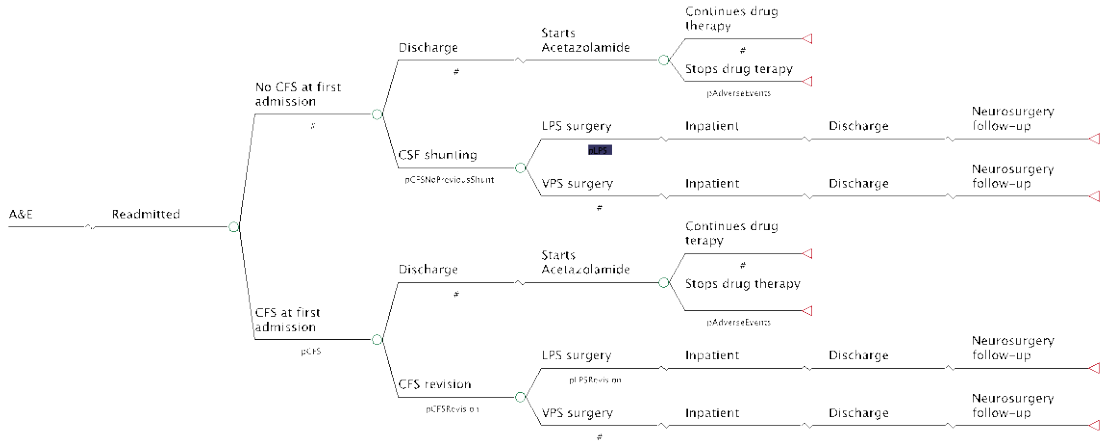
3 British National Formulary 2016 (https://bnf.nice.org.uk/medicinal-forms/acetazolamide.html). Last accessed 19th December, 2017.

Supplementary file 3

Figure to show the typical patient pathway



Supplementary file 4
Figure of the tree diagram to show the typical readmission pathway for patients



Supplementary file 5
Methods for the prediction health care costs in IIH.

For the first admission, the pathway assumed that all patients were referred to the accident and emergency department (Emergency room) via an optometry or optician practice who suspected papilledema. In the UK, the majority of these patients would be admitted to hospital, with a total length of stay being 2.7 days, as derived from the HES data (see results). Initial investigations at admission include one lumbar puncture, one brain imaging scan and venography (assumed to be 50% CT and 50% MRI). The majority of patients were discharged on acetazolamide, at a dosage of 1g per day, and 40% of these patients were assumed to discontinue drug therapy within a year due to adverse events[22]. Of the initial cohort of patients that were referred to the Emergency room, 6.6% had CSF diversion or shunting surgery and an average length of stay of 8.8 days (as derived from the HES data). Between 2002 and 2014, The Cambridge Shunt registry[18] reported 3000 shunt procedures, for all conditions including IIH, each year with 1400 procedures in adults, of which 53% were primary and 47% revisions; the placement location was recorded at 76.51% being Ventricular-; 7.47% Lumbar- and 1.39% other. The model therefore assumed a ratio of 10:1 ventricular:lumbar placement of the shunt device for IIH.

Costs associated with the first year follow up visits were estimated by assuming the following schedule: an ophthalmology appointment every 3 months (which is at fixed cost no matter what investigations are included); neurology appointment every four months and for patients who have undergone a neurosurgical procedure, one additional post-operative neurosurgery appointment.

The second pathway represents the likely care received for patients who were readmitted to hospital within the year following their diagnosis (supplementary file 4). This pathway assumes that readmitted patients who had previously undergone CSF diversion surgery have a higher probability (0.51) of requiring CSF revision surgery.[23] If no previous CSF diversion/shunt surgery was undertaken, the probability of having a CSF diversion surgery is

1% (derived from HES results). The pathway then assumed the same follow-up visit schedule as before with one additional neurosurgery follow-up visit for those patients who had surgery on readmission.

Supplementary File 6:

The age group of the IIH cohort (2002-2016).

Age (years)		Males	Females	Persons
		Number (%)		
	Under 13	855 (21.0%)	878 (4.6%)	1733 (7.5%)
	13-16	361 (8.9%)	1083 (5.7%)	1444 (6.2%)
	17-19	133 (3.3%)	1347 (7.1%)	1480 (6.4%)
	20-24	289 (7.1%)	3538 (18.5%)	3827 (16.5%)
	25-29	267 (6.5%)	3565 (18.7%)	3832 (16.5%)
	30-34	282 (6.9%)	2468 (12.9%)	2750 (11.9%)
	35-44	563 (13.8%)	3233 (16.9%)	3796 (16.4%)
	45-54	516 (12.7%)	1730 (9.1%)	2246 (9.7%)
	55-64	390 (9.6%)	726 (3.8%)	1116 (4.8%)
	65+	423 (10.4%)	535 (2.8%)	958 (4.1%)
	Total	4079	19103	23182

Supplementary File 7:

The ethnicity recorded by HES data of the IIH cohort (2002-2016), with a comparison made to the percentage ethnic groups in England and Wales in 2011.

Ethnicity	Males	Females	Persons	Percentage of total population
White	2904 (71.2%)	14419 (75.5%)	17323 (74.7%)	86.0%
Black/Black British	125 (3.1%)	751 (3.9%)	876 (3.8%)	3.3%
Asian/Asian British	197 (4.8%)	696 (3.6%)	893 (3.9%)	7.5%
Chinese	7 (0.2%)	20 (0.1%)	27 (0.1%)	0.7%
Mixed	48 (1.2%)	210 (1.1%)	258 (1.1%)	2.2%
Other	78 (1.9%)	267 (1.4%)	345 (1.5%)	1.0%
Unknown	720 (17.7%)	2740 (14.3%)	3460 (14.9%)	-

Supplementary File 8:

The regional location of the recorded home address, by Government Office Region (GOR), for each patient newly diagnosed with IIH (2002-2016) and their socio-economic deprivation quintile (based on Index of Multiple Deprivation 2010).

Region of residence (GOR)	**Male number (%)**	**Female number (%)**	**Total number (%)**
East of England	586 (14.4)	2784 (14.6)	3370 (14.5)
West Midlands	646 (15.8)	2686 (14.1)	3332 (14.4)
Yorkshire and Humber	627 (15.4)	2582 (13.5)	3209 (13.8)
South East	551 (13.5)	2254 (11.8)	2805 (12.1)
South West	365 (8.9)	2126 (11.1)	2491 (10.7)
North East	366 (9.0)	1931 (10.1)	2297 (9.9)
London	419 (10.3)	1877 (9.8)	2296 (9.9)
North West	333 (8.2)	1812 (9.5)	2145 (9.3)
East Midlands	179 (4.4)	1044 (5.)	1223 (5.3)
No Fixed Abode	7 (0.2)	7 (0.0)	14 (0.1)
Deprivation quintile			
1 – most deprived	1065 (26.1)	5682 (29.7)	6747 (29.1)
2	874 (21.4)	4515 (23.6)	5389 (23.2)
3	816 (20.0)	3498 (18.3)	4314 (18.6)
4	675 (16.5)	2918 (15.3)	3593 (15.5)
5 - Least deprived	627 (15.4)	2453 (12.8)	3080 (13.3)
Unknown	22 (0.6)	37 (0.6)	59 (0.3)

Supplementary File 9:

The number of admitted hospital episodes in the first year following a diagnosis of IIH.

Number of additional admitted hospital attendances in first year following the initial attendance for the diagnosis of IIH	Number of patients (% of total number of patients)
0	14504 (62.2)
1	4105 (17.7)
2	1916 (8.3)
3	962 (4.1)
4	519 (2.2)
5	349 (1.5)
6	261 (1.1)
7	180 (0.8)
8	92 (0.4)
9	76 (0.3)
10+	218 (0.9)

Supplementary file 10:

Number of births in the general population (aged 16-55) compared to those diagnosed with IIH between 1st January 2002 and 31st December 2015.

Number of births	General population (excluding IIH	IIH
1	2,927,954 (58.1%)	2,535 (50.8%)
2	1,633,387 (32.4%)	1,714 (34.33%)
3	376,778 (7.5%)	569 (11.4%)
4	77,495 (1.5%)	134 (2.7%)
5	15,841 (0.3%)	28 (0.6%)
6	3,598 (0.1%)	11 (0.2%)
7	865 (0.0%)	
8	197 (0.0%)	
9	46 (0.0%)	
10	7 (0.0%)	

Publication 2: Idiopathic intracranial hypertension: consensus guidelines on management

Manuscript title:
Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, Krishnan A, Chavda SV, Ramalingam S, Edwards J, Hemmings K, Williamson M, Burdon MA, Hassan-Smith G, Digre K, Liu GT, Jensen RH, Sinclair AJ. Idiopathic intracranial hypertension: consensus guidelines on management. J Neurol Neurosurg Psychiatry. 2018;89(10):1088-1100

Involvement:
I performed a literature review. I set up the specialty groups. I drafted the list of questions to be addressed. I wrote the first manuscript, and critically revised the manuscript.

Page number: 30

OPEN ACCESS

REVIEW

Idiopathic intracranial hypertension: consensus guidelines on management

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ABSTRACT

The aim was to capture interdisciplinary expertise from a large group of clinicians, reflecting practice from across the UK and further, to inform subsequent development of a national consensus guidance for optimal management of idiopathic intracranial hypertension (IIH).

Methods Between September 2015 and October 2017, a specialist interest group including neurology, neurosurgery, neuroradiology, ophthalmology, nursing, primary care doctors and patient representatives met. An initial UK survey of attitudes and practice in IIH was sent to a wide group of physicians and surgeons who investigate and manage IIH regularly. A comprehensive systematic literature review was performed to assemble the foundations of the statements. An international panel along with four national professional bodies, namely the Association of British Neurologists, British Association for the Study of Headache, the Society of British Neurological Surgeons and the Royal College of Ophthalmologists critically reviewed the statements.

Results Over 20 questions were constructed: one based on the diagnostic principles for optimal investigation of papilloedema and 21 for the management of IIH. Three main principles were identified: (1) to treat the underlying disease; (2) to protect the vision; and (3) to minimise the headache morbidity. Statements presented provide insight to uncertainties in IIH where research opportunities exist.

Conclusions In collaboration with many different specialists, professions and patient representatives, we have developed guidance statements for the investigation and management of adult IIH.

SCOPE

This is a consensus document to provide practical information for best practice in uniform investigation and treatment strategies based on current literature and opinion from a specialist interest group (SIG) for adult idiopathic intracranial hypertension (IIH). This should increase awareness of IIH among clinicians and improve outcomes for patients.

The target audience for this statement includes neurologists, ophthalmologists, neurosurgeons, radiologists, emergency medicine specialists, physicians, ear nose and throat specialists and other clinicians who investigate and manage IIH. It also contains information that will be of interest to those in primary care and other healthcare professionals.

The increasing economic burden of IIH has been highlighted by a number of groups.[1 2] Clear guidance will help educate the attending doctors to manage these patients appropriately. This will help reduce the repeat unsolicited emergency hospital attendances and reduce IIH-related disability. There are a number of ongoing clinical trials in IIH (https://www.clinicaltrials.gov/) and as evidence for medical and surgical management evolves in IIH this document will require timely updates.

BACKGROUND

IIH occurs predominantly in women and although the underlying pathogenesis is not fully understood, it has a striking association with obesity.[3] The combination of raised intracranial pressure, without hydrocephalus or mass lesion, normal cerebrospinal fluid (CSF) composition and where no underlying aetiology is found are accepted criteria for the diagnosis of IIH.[4] The overall age-adjusted and gender-adjusted annual incidence is increasing and was reported to be 2.4 per 100 000 within the last decade (2002–2014).[5]

The majority of patients presenting with IIH have symptoms that include a headache that is progressively more severe and frequent, as defined by International Classification of Headache Disorders, 3rd edition (ICHD-3) (figure 1).[6] The headache phenotype is highly variable and may mimic other primary headache disorders. Other symptoms may include transient visual obscurations (unilateral or bilateral darkening of the vision typically seconds), pulsatile tinnitus, back pain, dizziness, neck pain, visual blurring, cognitive disturbances, radicular pain and typically horizontal diplopia (figure 1A)[3]: none of which are pathognomonic for IIH.[7] Investigation and management depends on symptoms and signs and requires an interdisciplinary team approach.

For the individual patient, some can have permanent visual loss.[8] Chronic headache significantly impacts quality of life[9 10] with over half of patients with IIH reporting ongoing headaches at 12 months.[11]

Clinical uncertainty exists, and IIH can be misdiagnosed.[12] The 2015 Cochrane review has concluded that there is lack of evidence to guide

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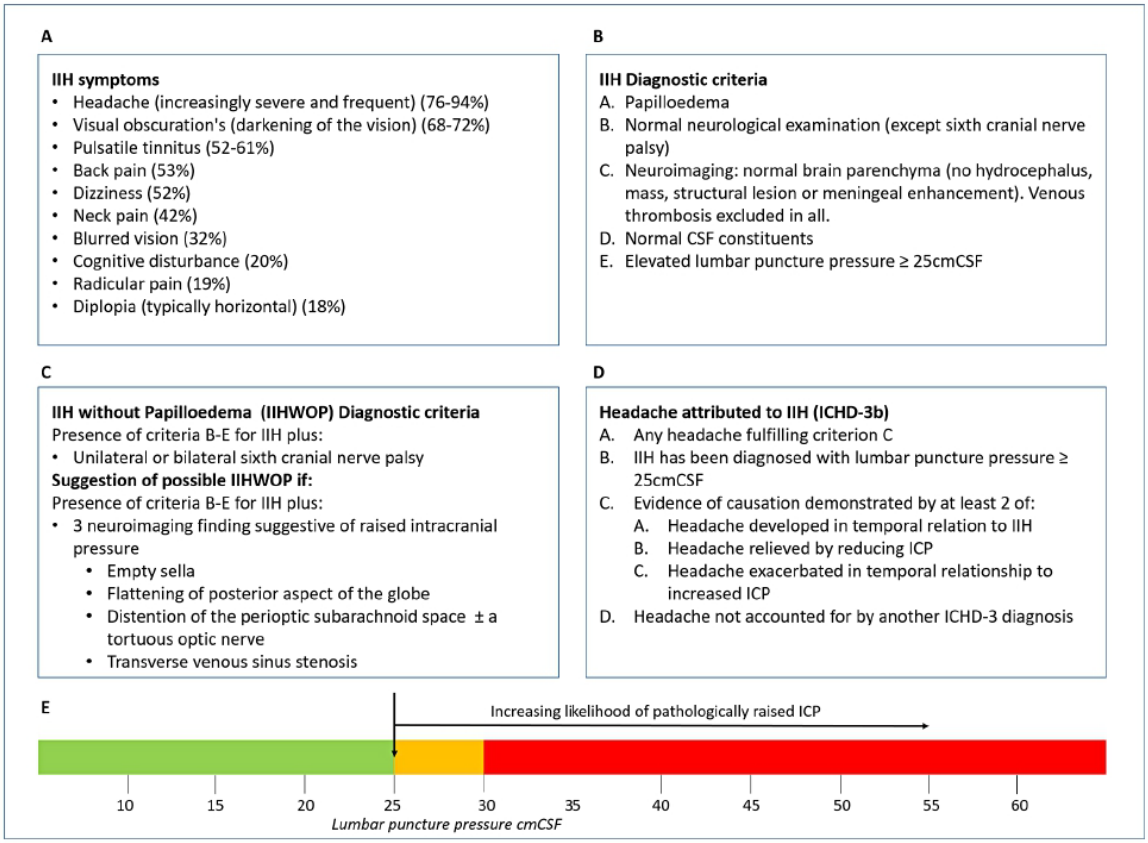

Figure 1 Consensus in diagnosing IIH. (A) Frequency of IIH symptoms reported, adapted from Markey *et al*.[3] (B) IIH diagnostic criteria, adapted from Friedman *et al*.[4] (C) IIHWOP diagnostic criteria, adapted from Friedman *et al*.[4] (D) Headache attributed to IIH, as described by the International Classification of Headache Disorders, 3rd edition (beta version) (ICHD-3 beta).[6] (E) Line figure detailing the consensus of the interpretation of LP opening pressure. Uncertainty: it needs to be recognised that this is a single LP OP measurement; and after raised ICP what is then a normal ICP for this population on repeat LP readings is unknown. CSF, cerebrospinal fluid; IIH, idiopathic intracranial hypertension; LP, lumboperitoneal.

pharmacological treatment in IIH.[13] Randomised clinical trials are currently infrequent in this field due to the rarity of the disease, the lack of understanding of the underlying pathological mechanisms and limited disease-modifying therapies.

METHODS

An SIG was formed, including neurology, neurosurgery, neuroradiology, ophthalmology, nursing, primary care doctors and patient representatives. All clinicians had expertise in managing IIH. An initial UK survey of attitudes and practice in IIH was sent to a wide group of consultants who investigate and manage IIH regularly: these included neurology, neurosurgery, neuro-ophthalmology and neuroradiology. A comprehensive systemic literature review was performed to assemble the foundations of the statements. Rigorous controlled data are sparse in IIH, and therefore, a consensus-based guide is presented. Questions were formulated (table 1). An anonymous modified Delphi process was used to obtain consensus on guidance statements. All statements below obtained consensus of 75% or above from the SIG and wider Delphi group. A completed AGREE statement is found as supplementary data (online supplementary appendix 1).

An international panel of experts in IIH (RHJ, GTL and KD) reviewed the document and a wider consultation was made with professional bodies namely the Association of British Neurologists (ABN), the Society of British Neurological Surgeons (SBNS), the Royal College of Ophthalmologists (RCOphth) and the British Association for the Study of Headache (BASH). Where there was disagreement in statement recommendations, these were debated within the SIG, and wording was altered accordingly.

Specifically, to improve local outcomes for patients with IIH, audit recommendations are enclosed (online supplementary appendix 2). This document will need to be revised regularly as new evidence emerges in the field of IIH. Definitions used in the guidance are presented in table 2.[14–17]

DIAGNOSTIC PRINCIPLES

For optimal investigation of patients with papilloedema, there must be clear communication between clinicians for seamless joint investigation between the various specialities. The aims of investigations of papilloedema are to:

1. find any underlying treatable cause in a timely manner
2. protect the vision and ensure timely re-examination when vision is at risk
3. enable onward care of the patient with the input from the most appropriate experienced clinician.

Q1 How should papilloedema be investigated? (figure 2)

► *Blood pressure* must be measured to exclude malignant hypertension, as defined as a diastolic blood pressure greater

Table 1 Questions formulated by the ABN IIH SIG on the diagnosis and management of IIH

Question number	
	Diagnostic principles
1	*How should papilloedema be investigated?*
	Management principles Principle one: treat the underlying disease
2	*What is the best way to modify the underlying disease to induce remission?*
	Principle two: protect the vision
3	*How should IIH be treated when there is imminent risk of visual loss?*
4	*What is currently the best surgical procedure for visual loss in IIH?*
5	*What other surgical procedures are performed for visual loss in IIH?*
6	*What is the current role of neurovascular stenting in acute IIH to prevent loss of vision?*
7	*What is the role of serial lumbar punctures in IIH?*
8	*What is the best drug treatment for IIH symptoms?*
9	*How should acetazolamide be prescribed?*
10	*Are there other drugs that are helpful in IIH?*
	Principle three: manage the headache
11	*What is the best way to manage headaches in* **newly diagnosed** *IIH?* (figure 4)
12	*What is the best approach to long-term headache management in IIH?*
13	*What therapeutic strategies are useful for headache in IIH?*
14	*How should medication overuse headache be approached?*
15	*Should CSF diversion surgery be used in patients with IIH with headache alone?*
16	*Should neurovascular stenting be used in patients with IIH with headache alone?*
17	*How should an acute exacerbation of headache be investigated in those who are already shunted?*
18	*How should an acute exacerbation of headache be treated in those who are already shunted?*
	Clinical care and managing IIH in pregnancy
19	*Are there any other chronic problems that need to be addressed in IIH?*
20	*What advice should be given regarding drug treatments in the pregnant patient with IIH?*
21	*What additional considerations for management are there in the pregnant patient with IIH?*
	IIHWOP
22	*How should IIHWOP be managed?*
	Follow-up and monitoring of IIH
23	*How should we follow-up and monitor these patients?*

ABN, Association of British Neurologists; CSF, cerebrospinal fluid; IIH, idiopathic intracranial hypertension; IIHWOP, IIH without papilloedema; SIG, specialist interest group.

Table 2 Definitions of the terms used in the guidance

Term	Definition
Adult	All patients above the age of 16 years old for the purpose of this statement.
Idiopathic intracranial hypertension (IIH)	Patients with raised ICP of unknown aetiology fulfilling the criteria set out in figure 1.
Fulminant IIH	Patients meeting the criteria for a precipitous decline in visual function within 4 weeks of diagnosis of IIH.[14]
Typical IIH	Patients who are female, of childbearing age and who have a body mass index (BMI) greater than 30 kg/m^2.
Atypical IIH	Patients who are not female, or not of childbearing age or who have a BMI below 30 kg/m^2. These patients require more in-depth investigation to ensure no other underlying causes (table 2).[15 25]
IIH without papilloedema	A rare subtype of IIH[16 17] and is seen in patients who meet all the criteria of definite IIH,[4] seen in figure 1, in the absence of papilloedema. The criteria have highlighted the importance of a pressure greater than 25 cm CSF and the necessity for additional features, which suggest pathologically raised ICP. Features such as sixth nerve palsy and MRI imaging features indicating raised ICP should be sought (box 1).
IIH in ocular remission	Patients that have been diagnosed as IIH, and the papilloedema has resolved. These patients may have ongoing morbidity from headache, but their vision is no longer at risk while there is no papilloedema.
Experienced clinician	Refers to any clinician, in the context of this guidance, who has confidence in their own experience of managing IIH.

than or equal to 120 mm Hg or systolic blood pressure greater than or equal to 180 mm Hg.[18]

- Ophthalmology examination: all patients should have papilloedema confirmed and an assessment made of the imminent risk to their visual function. The following should be recorded in the presence of papilloedema:
  - visual acuity
  - pupil examination
  - intraocular pressure (to exclude hypotony, a rare cause for disc swelling)
  - formal visual field test (perimetry)
  - dilated fundal examination to grade the severity of the papilloedema and exclude ocular causes for disc swelling.

Where possible, document the fundus picture with drawings and document key findings on the optic nerve head (hyperaemia, haemorrhages, cotton wool spots, obscuration of the vessels and so on). Photographs and/or optical coherence tomography (OCT) imaging are useful. Where visual function is found to be threatened, regular ophthalmic examination must occur because this will influence timely management (see *23 How should we follow-up and monitor these patients?* in table 3).

Uncertainty

Where there is diagnostic uncertainty regarding papilloedema see the differential diagnosis of papilloedema and pseudopapilloedema in supplementary table 1, an experienced clinician should be consulted early before invasive tests are performed.

- *Neurological examination*
  - Record cranial nerve examination. Where IIH is suspected, typically there should be no cranial nerve involvement other than sixth cranial nerve palsy/palsies.
  - Should other cranial nerves and/or other pathological findings be involved, an alternative diagnosis should be considered.
- *Neuroimaging*
  - Urgent MRI brain within 24 hours; if unavailable within 24 hours, then urgent CT brain with subsequent MRI brain if no lesion identified.
  - There should be no evidence of hydrocephalus, mass, structural, vascular lesion and no abnormal meningeal enhancement.[4]

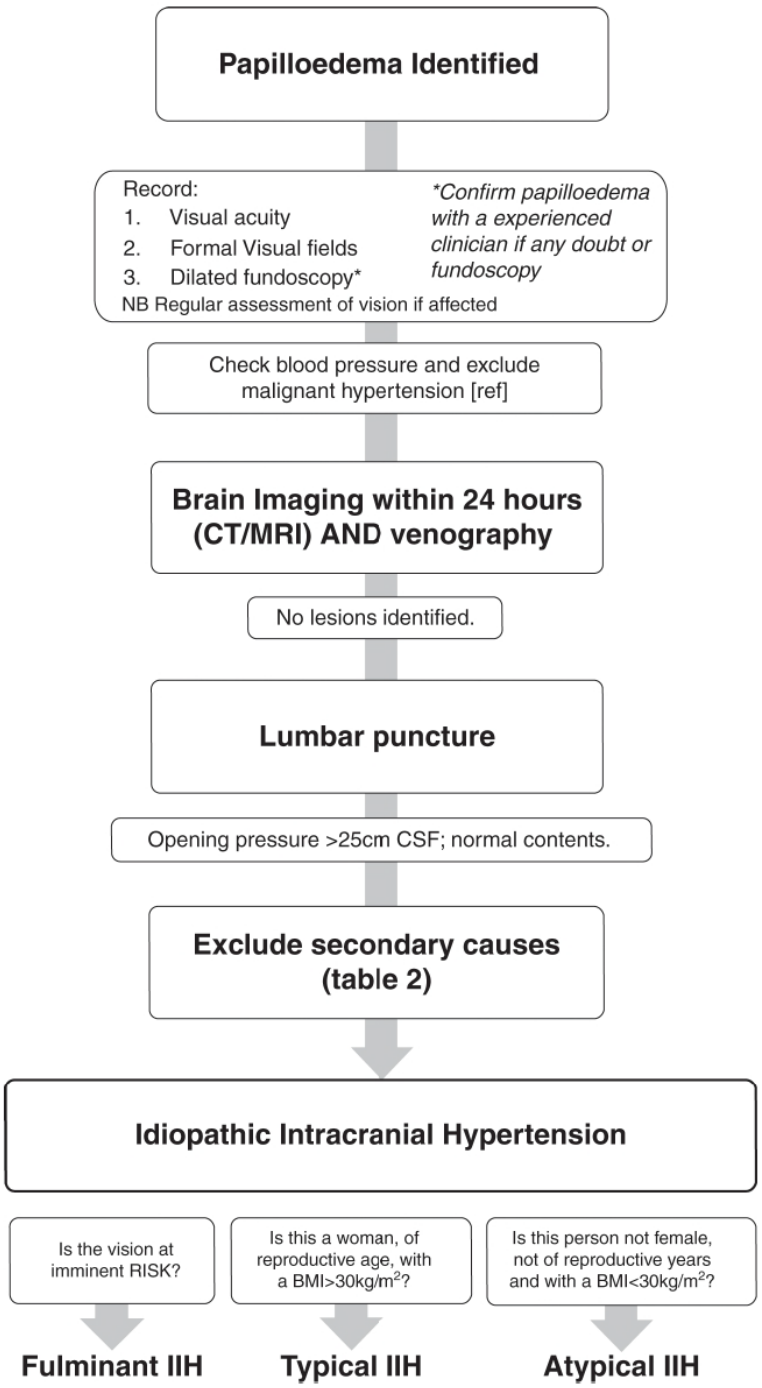

Figure 2 A flow diagram of investigation of papilloedema. BMI, body mass index; IIH, idiopathic intracranial hypertension.

- CT or MR venography is mandatory to exclude cerebral sinus thrombosis within 24 hours.
- Characteristics of raised intracranial pressure may be seen on neuroimaging (box 1); these are not pathognomonic of IIH.[19–22]

Uncertainty

We recognise the difficulties in the interpretation of cerebral venography. Where there is diagnostic uncertainty regarding interpretation of the venogram findings , an experienced radiologist should be consulted.

► *Lumbar puncture*

- Following normal imaging, all patients with papilloedema should have a lumbar puncture to check opening pressure and ensure contents are normal.
- The lumboperitoneal (LP) opening pressure should be measured in the lateral decubitus position.[4] Following

Table 3 Associations that have been reported as causing raised Intracranial pressure[15 25]

Haematological	Anaemia Polycythaemia vera
Obstruction to venous drainage	Cerebral venous sinus thrombosis
	Jugular vein thrombosis
	Superior vena cava syndrome
	Jugular vein ligation following bilateral radical neck dissection
	Increased right heart pressure
	Arteriovenous fistulas
	Previous infection or subarachnoid haemorrhage causing decreased CSF absorption
Medications	Fluoroquinolones
	Tetracycline class antibiotics
	Corticosteroid withdrawal
	Danazol
	Vitamin A derivatives (including isotretinoin and all-transretinoic acid)
	Levothyroxine
	Nalidixic acid
	Tamoxifen
	Ciclosporin
	Levonorgestrel impant
	Lithium
	Growth hormone
	Indomethacin
	Cimetidine
Systemic disorders	Chronic kidney disease/renal failure
	Obstructive sleep apnoea syndrome
	Chronic obstructive pulmonary disease
	Systemic lupus erythematosus
	Psittacosis
Endocrine	Addison's disease
	Adrenal insufficiency
	Cushing's syndrome
	Hypoparathyroidism
	Hypothyroidism
	Hyperthyroidism
Syndromic	Down syndrome
	Craniosynostosis
	Turner syndrome

needle insertion into the CSF space, the pressure recording should occur with the patient relaxed and the legs extended. The CSF level should be allowed to settle before taking the reading.

- The CSF analysis should be tailored to the presentation but should at a minimum include CSF protein, glucose and cell count.
- A clear explanation of the LP should be given to patients to reduce fear and anxiety about the procedure.
- Where difficulty exists in performing the LP, the length of the procedure should be balanced by the comfort of the individual patient.
- Should the LP not be successful, a guided LP could then be considered (ultrasound or X-ray).[23 24]
- The diagnostic criteria mandate a cut-off opening pressure of >25 cm CSF for diagnosing IIH.[4]
- The LP opening pressure should not be interpreted in isolation when diagnosing IIH.

Uncertainties

Clinicians debate the absolute LP opening value of 25 cm CSF as diagnostic of IIH. This was recognised by Friedman and colleagues.[4] Below the cut-off of 25 cm CSF, there are reservations as to the likelihood of diagnosing IIH. As highlighted in figure 1E, the SIG clinicians' opinions are that there is an increasing likelihood of the significance of LP OP measurement, as it rises. The LP OP is a single measurement, and it is widely recognised that there is a diurnal and wide variation in CSF pressure.

Where the LP OP does not fit the clinical picture, it should be interpreted with caution. A repeat LP may be considered or intracranial ICP monitoring could be considered. There is no current evidence to dictate how much CSF is recommended to be drained or what the closing pressure should be.

► *Exclusion of all other secondary causes of raised ICP*
  - All should have a careful history taken to exclude any possible secondary causes that have previously been linked to raised intracranial hypertension (table 2), although the causal link with IIH and a number of diseases and medications is not clear.[15 25]
  - All patients should have a full blood count performed to exclude anaemia.[26 27]
  - Where patients are deemed to be atypical (table 1), other additional blood tests may be considered to exclude secondary causes.
  - Where patients are deemed to be atypical (table 1), additional neuroimaging might be considered. These may include more proximal imaging of the neck vasculature to exclude internal jugular obstruction.

Uncertainty

In those with IIH, there is no clear evidence of a contraindication for using medications (including the oral contraceptive) that have been previously been reported to be casually associated with secondary pseudotumour.

Where uncertainty exists, patients who have atypical aspects could be referred for an opinion from a experienced clinician familiar with IIH.

MANAGEMENT PRINCIPLES

For optimal management of patients with IIH, there must be clear communication between clinicians for seamless joint care between the various specialties (figure 3). Weight loss reduces ICP and has been shown to be effective in improving papilloedema and headaches.[28] The main principles of management of IIH are:

1. to treat the underlying disease
2. to protect the vision
3. to minimise the headache morbidity.

Twenty-three questions were formulated to cover the three principle domains of management in IIH (table 1).

Primary principle for IIH management: modify the underlying disease through weight loss

Q2 What is the best way to modify the disease to induce remission?

Weight loss is the only disease-modifying therapy in typical IIH.[28]

► Once definite IIH is diagnosed, all patients with a BMI >30 kg/m^2 should be counselled about weight management at the earliest opportunity. This should be done with sensitivity.

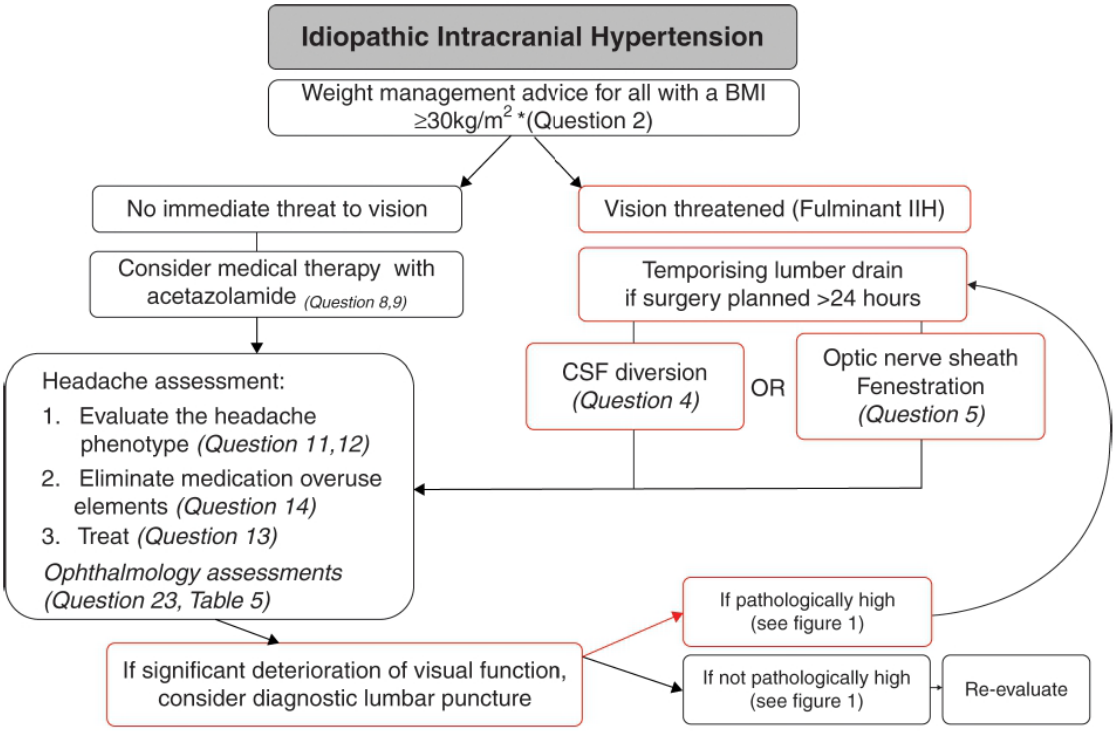

Figure 3 Management flow chart of diagnosed IIH. BMI, body mass index; CSF, cerebrospinal fluid; IIH, idiopathic intracranial hypertension.

- The amount of weight loss required to put the disease into remission is not known. It is noted that in the year preceding a diagnosis of IIH is associated with 5%–15% wt gain,[29] and up to 15% of weight loss was required to put IIH into remission in one cohort.[28]
- Patients should be referred to a community weight management programme or a hospital-based weight programme.

Uncertainty

Maintained weight loss is difficult to achieve, and the optimal approach to achieving long-term weight management has not yet been clearly established.[30 31] If weight loss cannot be achieved by the patients themselves, the first step would be professional help through a structured diet. There is an increasing role for bariatric surgery for sustained weight loss,[31 32] and for use in IIH, more prospective controlled evidence is required.[2 33 34] For those who are not obese secondary causes should be revisited (box 1), and the role of weight gain/loss remains uncertain.

Second principle for IIH management: protect the vision

Q3 How should IIH be treated when there is imminent risk of visual loss?

- Where there is evidence of declining visual function, the acute management to preserve vision is surgical.
- A temporising measure of a lumbar drain could be useful to protect the vision while planning urgent surgical treatment.
- There is evidence that many of the surgical procedures, such as CSF diversion and optic nerve sheath fenestration (ONSF), work well in the short term.[35] While they are working, the underlying disease should be modified with weight loss (see *1. What is the best way to modify the disease to induce remission?* in table 3).

Uncertainty

In the absence of high class evidence, we do not recommend the use of corticosteroids for fulminant IIH at this time, and indeed a prolonged treatment course of corticosteroids would not be recommended due to weight gain.

Q4 What is currently the best surgical procedure for visual loss in IIH?

- In the UK, the preferred surgical procedure is neurosurgical CSF diversion (see *5. What other surgical procedures are performed for visual loss IIH?*).
- Where possible. it should be performed by a experienced clinician with an interest in CSF disorders.

Box 1 Typical neuroimaging features found in raised intracranial pressure[19–22]

Neuroimaging features of raised ICP:
- empty sella
- partially empty sella/decreased pituitary height
- increased tortuosity of optic nerve
- enlarged optic nerve sheath (perioptic subarachnoid space)
- flattened posterior globe/sclera
- intraocular protrusion of optic nerve head
- attenuation of the cerebrovenous sinuses including bilateral transverse sinus stenosis or stenosis of a dominant transverse sinus.

Note: Enhancement with IV contrast of the optic nerve sheath has been reported. Additionally, ventricle size in IIH is typically normal however many reports consider the ventricles to be slit-like.

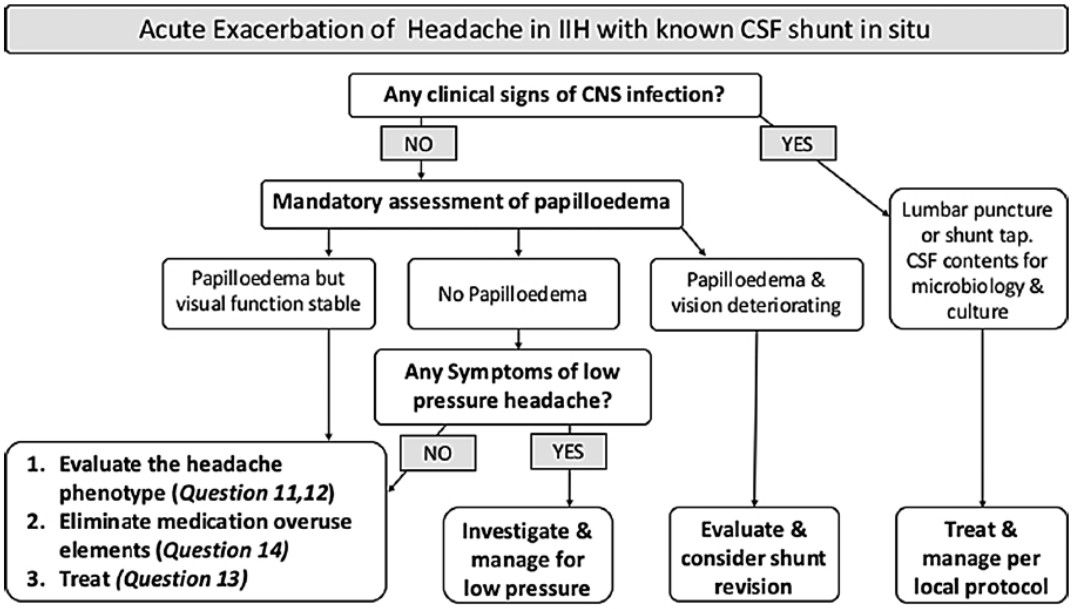

Figure 4 Flow chart of acute exacerbation of headache in IIH with known CSF shunt in situ. CSF, cerebrospinal fluid; IIH, idiopathic intracranial hypertension.

- Ventriculoperitoneal (VP) should be the preferred CSF diversion procedure for visual deterioration in IIH, due to lower reported revisions per patient.[2]
- An LP shunt could also be used.
- It is best practice to use neuronavigation to place VP shunts.
- All patients in the UK should be counselled that they should inform the Driver and Vehicle Licensing Agency following VP shunt placement.
- Adjustable valves with antigravity or antisiphon devices should be considered for use to reduce the risk of low pressure headaches.

Uncertainty

The literature pertaining to shunt type is observational and mainly case series based. Complications of shunts include abdominal pain, shunt obstruction, migration and infection, low pressure headaches, subdural haematoma and tonsillar herniation.[36 37] There is a low, but present, mortality rate with CSF diversion; these figures do not come from IIH cohorts.

Q5 What other surgical procedures are performed for visual loss in IIH?

ONSF is performed more frequently in Europe and the USA and rarely in the UK. ONSF is reported to have less complications than CSF diversion, and there have been no reports of mortalities in the literature. The reported temporary adverse effects include double vision, ansiocoria and optic nerve head haemorrhages. Very rarely more permanent sequelae that include branch and central retinal artery occlusions have been reported. Some consider ONSF as the first treatment step in malignant fulminant cases and eventually also for those with asymmetric papilloedema causing visual loss in one eye.[38] If this procedure fails, then the more invasive CSF diversion can be considered. ONSF should be performed by an experienced clinician trained in this technique.

Uncertainty

The literature is observational and mainly case series based.[38 39] Treatment failure rates include worsening in vision after a period of stabilisation in 34% of patients at 1 year and 45% at 3 years. There is also failure to improve headache in one third to one-half.[39]

Q6 What is the current role of neurovascular stenting in acute IIH to prevent loss of vision?

Improvements in venography imaging now detail that many with IIH have anatomical abnormalities of the cerebral venous sinus system. These include stenosis of the dominant or both transverse sinus. The stenosis may result from intrinsic dural sinus anatomy or extrinsic compression by the increased intracranial pressure and reducing ICP can led to resolution of stenosis. The degree of stenosis does not appear to uniformly correlate with intracranial pressure or visual loss.[40] Neurovascular stenting has been reported, in a number of series, to lead to an improvement in symptoms of intracranial hypertension. Complications of the procedure include a short-lived ipsilateral headache in many, stent-adjacent stenosis that require retreatment in a third and in rare cases vessel perforation leading to acute subdural haematoma, stent migration and thrombosis.

- The role of neurovascular stenting in IIH is not yet established.
- Long-term antithrombotic therapy is required for longer than 6 months following neurovascular stenting treatment.

Uncertainty

The literature is observational and mainly case series based, and there is no long-term data regarding efficacy and safety. The role of neurovascular stenting in IIH to preserve rapidly deteriorating vision is not yet established, as there is a lack of quality data in this area. It may be useful for highly selected patients with IIH with venous sinus stenosis with an elevated pressure gradient and elevated ICP in whom traditional therapies have not worked.[40 41]

Q7 What is the role of serial lumbar punctures in IIH?

The relief from a LP is typically short lived as CSF is secreted from the choroid plexus at a rate of 25 mL/hour and consequently the volume removed in a so-called therapeutic tap is rapidly replaced.[42]

- Serial lumbar punctures are not recommended for management of IIH.
- Despite the relief of headache in nearly three quarters of patients,[43] LPs are associated with significant anxiety in many patients and can led to acute and chronic back pain in some patients.[7 43]

Q8 What is the best drug treatment for IIH symptoms?

The current Cochrane review on IIH management reported on the use of acetazolamide, a carbonic anhydrase inhibitor, in IIH. It concluded: 'the two included RCTs showed modest benefits for acetazolamide for some outcomes, there is insufficient evidence to recommend or reject the efficacy of this intervention, or any other treatments currently available, for treating people with IIH'.[13]

The two studies included in this review were:

a. The IIH Treatment Trial[44] reported the use of acetazolamide with a low-sodium weight-reduction diet compared with diet alone resulted in modest improvement in visual field function in patients with mild visual loss. The IIHTT also reported improved quality of life outcomes at 6 months with acetazolamide.[45]
b. Ball *et al*[46] failed to show a treatment effect. Importantly, 48% discontinued acetazolamide due to adverse effects.

- Acetazolamide could be prescribed for those with IIH symptoms.
- All females with IIH when commencing any new medical therapy (whether IIH specific or headache related) must be counselled regarding side effects and potential teratogenetic risks (see *21. What additional considerations for management are there in the pregnant patient with IIH?* in table 3).
- Drug therapies may need to be altered due to adverse side effects, lack of efficacy, possible potential teratogenic effects in pregnancy or patient preference.

Uncertainty

In view of the limited evidence as reported by the 2015 Cochrane review[13] and the side effect profile, not all clinicians in the UK prescribe acetazolamide for IIH.

Q9 How should acetazolamide be prescribed?

- The IIHTT used a maximal dose of 4 g daily, with 44% of participants achieving 4 g/day, and the majority tolerating 1 g/day.[47] Ball *et al*[46] identified that 48% discontinued at mean doses of 1.5 g due to side effects.
- A popular starting dose of acetazolamide is 250–500 mg twice a day, with the majority of clinicians titrating the daily dose up.
- Patients should be warned of the adverse side effects of acetazolamide that are well recognised and include increased risk of diarrhoea, dysgeusia, fatigue, nausea, paraesthesia, tinnitus, vomiting, depression and rarely renal stones.
- There is no consensus over the use of normal release and modified release acetazolamide.

Uncertainties

The optimal dose of acetazolamide is not established. The licencing information regarding acetazolamide recommends periodic monitoring of serum electrolytes; however, there is no consensus on the timing of monitoring.

Q10 Are there other drugs that are helpful in IIH?

Topiramate has carbonic anhydrase activity and can suppress appetite. It has been compared with acetazolamide in an uncontrolled open label study for IIH.[48] Participants were alternately assigned to the treatments, not randomly, and there was no placebo control group. There is evidence of efficacy of topiramate in treating migraine.[49]

- There may be a role for topiramate in IIH with weekly dose escalation from 25 mg to 50 mg bd.
- Where topiramate is prescribed, women must be informed that it can reduce the efficacy of the contraceptive pill/oral contraceptives and other hormonal contraceptives.
- When topiramate is prescribed, women must be counselled regarding side effects (including depression and cognitive slowing) and potential teratogenetic risks.

Uncertainties

The role of other diuretics such as furosemide, amiloride and coamilofruse are not certain but are used by some as alternative therapies.

Third principle of IIH management: reduce headache disability

Raised ICP can drive headaches, which may be very severe at presentation.[11] Despite significant headache morbidity in IIH, there are no randomised controlled trials to guide headache management in IIH.

Q11 What is the best way to manage headaches in newly diagnosed IIH?

- Patients must be informed, at the earliest opportunity, of the potential issues of painkiller overuse that can lead to medication overuse headache (use of simple analgesics on more than 15 days per month or opioids, combined preparations or triptan medication on greater than 10 days per month for more than 3 months).[6]
- Short-term painkillers may be helpful in the first few weeks following diagnosis. These could include non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol. Indomethacin may have some advantage due to its effect of reducing ICP.[50] Caution is required with potential side effects of NSAIDs, and gastric protection may be needed.
- Opioids should not be prescribed for headaches.[51]
- Greater occipital nerve blocks maybe considered helpful by some, but there is a lack of evidence and consensus.
- Acetazolamide has not been shown to be effective for the treatment of headache alone.
- Lumbar punctures are not typically recommended for treatment of headache in IIH (see *7. What is the role of serial lumbar punctures in IIH?* in table 3).

Uncertainty

There is no evidence to support the optimal managing of headache in acute IIH.

Q12 What is the best approach for long-term headache management in IIH?

The pattern of headache in IIH often changes over time and needs careful assessment. There is frequently a mixed headache phenotype: headache attributed to IIH, migraine, medication overuse headache, tension-type headache, headache attributed

to low CSF pressure and headache attributed to iatrogenic Chiari malformation secondary to CSF shunting.[52 53]

- A multidisciplinary team approach could be considered including, ideally, an assessment by an experienced clinician with an interest in headache management.
- In patients with IIH, the headache phenotype should be assessed. Headache therapies should be tailored to the headache phenotype.
- IIH patients with headache need clear explanation of how their headaches change over time and how to minimise the risks of developing medication overuse headache.
- Early introduction of preventative medications (migraine preventatives) should be considered as these can take 3–4 months to reach maximal efficacy.

Uncertainty

There is no evidence to support the optimal managing of headache in established IIH.

Q13 What therapeutic strategies are useful for headache in IIH?

Migrainous phenotype is noted in 68% of IIH patients with headache.[54] Despite the lack of clinical trials, the use of migraine therapies in IIH patients with migraine headaches may be useful. Headaches with migrainous features include moderate to severe pain that maybe throbbing with photophobia, phonophobia, nausea and movement intolerance.

- Migraine attacks may benefit from triptan acute therapy used in combination with either a NSAID or paracetamol and an antiemetic with prokinetic properties.[51] Their use should be limited to 2 days per week or a maximum of 10 days per month.[55 56]
- Migraine preventative strategies could also be tried. These are most likely to be effective in those in whom the ICP is settling and also in those whom the papilloedema has resolved (IIH in ocular remission).
- National Institute of Health and Clinical Excellence guidelines for migraine prevention therapy is useful.[51]
- Caution must be observed before selecting drugs that could increase weight (beta blockers, tricyclic antidepressants, sodium valproate, pizotifen and flunarizine) or those that could exacerbate depression, a frequent comorbidity in IIH (beta blockers, topiramate and flunarizine).
- Topiramate (see *10. Are there other drugs that are helpful in IIH?* in table 3) may help with weight loss by suppressing appetite and have an effect on reducing ICP through carbonic anhydrase inhibition. Patients need to be cautioned about potential side effects of depression, cognitive slowing, reduction of the efficacy of the contraceptive pill/oral contraceptives and potential of teratogenic effects.
- Where topiramate has excessive side effects, zonisamide may be an alternative.[49]
- In patients with migraine, candesartan can be a useful alternative to a beta blocker due to its lack of weight gain and depressive side effects.[57] Alternatively, venlafaxine is weight neutral and helpful with depression symptoms.[58]
- Botulinum toxin A may be useful in those with coexisting chronic migraine[59]; there are no studies of botulinum toxin A in IIH.
- As with treatment of migraine, preventative drugs need to be started slowly and increased to a therapeutic tolerated dose for 3 months to enable a therapeutic trial.
- Similar to the treatment of migraine, many of these drugs are used off label in IIH.
- Lifestyle advice should be given with all headache disorders, as these can have considerable impact on the disease course. Strategies should be implemented to limit caffeine intake. Ensure regular meals and adequate hydration, exercise programme and sleep hygiene. Behavioural and stress management techniques can be implemented such as yoga, cognitive–behavioural therapy and mindfulness.

Uncertainty

There are no clinical trials as yet in the treatment of headache alone in IIH.

Q14 How should medication overuse be approached?

Medication overuse is a common issue for patients with IIH.[11] Successfully removing excessive analgesic use significantly improves headaches.[60] Additionally, if not addressed, MOH may prevent the optimisation and effectiveness of preventative treatments.

- Non-opioids and triptan medications may be stopped abruptly or weaned down within a month.[60]
- Opioid medications should be gradually removed, with at least 1 month painkiller free to determine effectiveness[61]

Uncertainty

The most effective strategies to facilitate acute analgesic medication withdrawal are not fully established.[56]

Q15 Should CSF diversion surgery be used in patients with IIH with headache alone?

Where papilloedema has resolved, typically, the ICP will be normalising, and conservative treatment strategies should be employed. CSF shunting to exclusively treat headache in IIH has limited evidence. Following CSF diversion 68% will continue to have headaches at 6 months and 79% by 2 years.[36] Twenty-eight per cent can develop iatrogenic low pressure headaches,[36] although this figure will vary depending on shunt and valve type.

- CSF diversion is generally not recommended as a treatment for headache alone in IIH.
- CSF diversion procedures for the management of headaches should only be carried out in a multidisciplinary setting and following a period of intracranial pressure monitoring.

Uncertainty

Patients with IIH often have coexisting migrainous headaches superimposed on the headaches secondary to raised intracranial pressure. Failure to optimise the ICP may render the migrainous headache difficult to treat.

Q16 Should neurovascular stenting be used in patients with IIH with headache alone?

The literature detailing stenting typically does not clearly separate the cohorts of IIH into those with visual loss, those with headaches alone and those with both. They typically also do not separate those with acute IIH, those with chronic IIH and those with IIH in ocular remission. Another major limitation is that case series are non-randomised; typically, they do not detail morphological stenosis type; they tend to be small in size with selection bias, and there is a lack of long-term follow-up.[62]

- Neurovascular stenting is not currently a treatment for headache in IIH.

Table 4 Consensus of follow-up intervals for patients with idiopathic intracranial hypertension (IIH) based on their papilloedema grade and their visual field status

Papilloedema grade	Visual field status: Normal	Affected but improving	Affected but stable	Affected but worsening
Atrophic			4–6 months	Within 4 weeks
Mild	6 months	3–6 months	3–4 months	Within 4 weeks
Moderate	3–4 months	1–3 months	1–3 months	Within 2 weeks
Severe		1–3 months	Within 4 weeks	With 1 week

Note: Once papillodema has resolved, visual monitoring within the hospital services may no longer be required. However, caution in those patients who were asymptomatic at presentation, as they will likely be asymptomatic if a recurrence occurs and longer term follow-up, may need to be considered.

Uncertainty

Patients with IIH often develop migrainous headaches superimposed on the headaches secondary to raised intracranial pressure. While CSF diversion procedures have not been shown to be effective for the management of headaches, this may be attributable to the migrainous component not being optimally addressed. Conversely, failure to optimise the ICP (with a CSF diversion procedures) may render the migrainous headache difficult to treat. CSF diversion procedures for the management of headaches should only be carried out in a multidisciplinary setting and following a period of intracranial pressure monitoring.

Management of headaches in the shunted patient with IIH

Shunted patients with IIH may have significant headache morbidity, and shunt failures and overdrainage should always be considered. Understanding the underlying causes may guide management. Shunt revision should not routinely be undertaken unless there is papilloedema and a risk of visual deterioration. Many of these patients may be in ocular remission, as with chronic IIH headaches, conservative management with migraine therapies and treatment of medication overuse should be tried initially. Patients may need assessment by a experienced clinician who routinely manage headache. Medication refractory patients should be managed in a specialist headache service and discussed within a multidisciplinary setting for consideration of ICP monitoring.

Q17 How should an acute exacerbation of headache be investigated in those who are already shunted? (figure 4)

- For all shunted patient with IIH presenting with an acute exacerbation of headaches,funduscopy is mandatory to establish if papilloedema exists and where visual function (including formal visual fields) is documented to be worsening, then surgical intervention may be required. For those with atrophic optic nerves further care should be taken to establish whether the headache is secondary to raised intracranial pressure.
- In those where there is suspicion of infection that may be worsening the headache, CSF should be obtained for microbiological evaluation and any underlying resultant infection appropriately treated.
- A diagnostic lumbar puncture should not be routinely performed in the absence of papilloedema (unless suspicion of infection, see above)
- In those with papilloedema, some may choose to perform a diagnostic LP. This may be helpful to establish ICP level and may have implications for management choices.
- CT imaging and shunt X-ray series should not routinely be considered for those without evidence of papilloedema, as these investigations do not alter management.[63 64]
- In some ICP, monitoring may be useful.

Q18 How should an acute exacerbation of headache be treated in those who are already shunted? (figure 4)

- For patients without current papilloedema or imminent risk to vision, shunt revision is not recommended.
- In shunted patients with deteriorating headaches, low pressure headache and shunt over drainage should be considered.
- In established overdrainage or low CSF pressure, consideration should be given to the valve settings or tying the shunt off.
- In the absence of shunt over drainage headache management should follow the section above (see *13. What therapeutic strategies are useful for headache in IIH?* in table 3 and figure 4: Manging acute exacerbation of headache in IIH).
- Consider medication overuse headache as a cause of acute exacerbation in shunted patients.[65]

Clinical care

Q 19 Are there any other chronic problems that need to be addressed in IIH?

- All of these patients require recognition that they have been diagnosed with a rare disease and need appropriate support to deal with the psychological burden of living with a chronic condition.
- The patient with IIH may have significantly higher levels of anxiety and depression and a lower quality of life.[9 45 66] This may be as a response to chronic pain. This needs recognition and appropriate management.
- Sleep apnoea is frequently reported in this group,[67] and referral to respiratory service may be appropriate.
- Polycystic ovary syndrome may coexist.[68]
- Cognitive dysfunction may coexist.[69]

Managing IIH in pregnancy

Q20 What advice should be given regarding drug treatments in the pregnant patients with IIH?

- A clear risk−benefit assessment regarding the necessity of acetazolamide treatment during pregnancy should be discussed with the patient as perinatal exposure in rodents has reported teratogenic effects.[70 71]
- With the limited evidence, it is difficult to make any safe recommendations on using acetazolamide during pregnancy and its manufacturers do not recommend it use.[72]
- Topiramate should not be used in pregnancy. There is clear evidence of a higher rate of fetal abnormalities following its use.[73]
- If a patient on topiramate becomes pregnant, they should reduce and discontinue it as soon as possible in line with manufacturers recommendations.
- A clear risk−benefit assessment regarding the necessity of headache treatment during pregnancy should be discussed with the patient as many of the regularly used headache medications are not recommended in pregnancy.

Q21 What additional considerations for management are there in the pregnant patient with IIH?

- Multidisciplinary communication among relevant experienced clinicians should occur throughout pregnancy, peridelivery and in the postpartum period.
- No specific mode of delivery should be suggested based on the fact there is a previous diagnosis of IIH.
- If not already under a weight management programme, consider referral to a weight service, so that weight gain is appropriate for gestational age of fetus as described by the American College of Obstetricians and Gynaecologists 2013 Guidelines.[74]
- Increased outpatient observation may be helpful to reassure other healthcare professionals and patients during this period.
- *How should an acute exacerbation of IIH, with imminent risk to vision be managed in pregnancy?*
- If the IIH is active with imminent risk of vision loss, then some would consider serial lumbar punctures as a temporising measure only until longer term measures, such as CSF diversion or ONSF, can be implemented.
- Those with imminent risk of vision loss at time of delivery should be managed in a specialist centre.

IIH without papilloedema

Q22 How should IIHWOP be managed?

In patients with IIHWOP, risk of vision loss has not been identified and does not seem to develop over the disease course. Visual phenomenon such as photopsia, diplopia (from sixth nerve palsy) and functional visual field loss are common.[75]

Headache is the principal morbidity in these patients.

- Once definite IIHWOP is diagnosed, all patients should be managed as typical IIH and counselled about weight management (see 2. *What is the best way to modify the disease to induce remission?* in table 3).
- Management of headache should be the same as typical IIH (see: Third principle of IIH management: reduce headache disability).
- Surgical management to control elevated intracranial pressures in IIHWOP should not routinely be considered unless advised by experienced clinicians within the multidisciplinary team setting.

Follow-up and monitoring of IIH

Q23 How should we follow-up and monitor these patients?

Any patient with papilloedema should have the following documented[24]:

1. visual acuity
2. pupil examination
3. formal visual field assessment
4. dilated fundal examination to grade the papilloedema.
5. BMI calculation.
   - Formal documentation of the optic nerve head appearance, such as serial photographs or OCT imaging, is useful. There are increasing reports of the utility of transorbital ultrasound to measure optic nerve sheath diameter; however, there are considerable differences across studies on the cut-off values used as well as the efficacy of ultrasound to predict ICP.[76]
   - All patients with or without papilloedema should have an assessment of their headache to include the features of the headache/s (to aide characterisation of the headache), headache frequency and severity and frequency of analgesic use.
   - A validated headache disability score such as HIT 6 may be useful.
   - Recommendations for follow-up intervals is seen at table 4. Should there be worsening of the visual fields or papilloedema, then outpatient review should be expedited.

CLOSING STATEMENT

In collaboration with many different experienced clinicians, professions and patient representatives, we have developed guidance statements for the investigation and management of adult IIH. We recognise that we were limited by the lack of high-quality evidence for the majority of the statements made and that a consensus-based approach could give authority to singular opinion. With a view to mitigate this, we have sought international expert review (GTL, RHJ and KD) and review by professional bodies (ABN, BASH, RCOphth and SBNS). Following review, a few points were upheld by the SIG such as the definition of typical IIH being diagnosed as obese and not just overweight (BMI >25 kg/m^2), which differs from current published diagnostic criteria.[4] As this document is aimed at a wide audience including non-IIH specialist, we wished to create criteria whereby the majority of patients with IIH would be correctly diagnosed. Hence, we needed to emphasise those patients in whom uncertainty could exist and referral to an experienced clinician maybe required. It was also highlighted that compared with our European and North American colleagues, there are few centres in the UK that perform ONSF for IIH.

These statements are not mandatory recommendations but are intended to be used as a guide for doctors who investigate and treat IIH. Despite the limitations of consensus-based methods, these statements reflect an up-to-date consensus to guide the clinician and serve our patients. Quality prospective research is required for all areas of uncertainties highlighted in this document to improve clinical outcomes for our patients with IIH.

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Publication 3: Evaluation and management of adult idiopathic intracranial hypertension

Manuscript title:
Mollan SP, Hornby C, Mitchell J, Sinclair AJ. Evaluation and management of adult idiopathic intracranial hypertension. Pract Neurol. 2018;18(6):485-488.

Involvement:
I drafted and refined the aide-mémoire, based on the key points from the consensus guideline document. I liaised with IIH UK to have them printed and disseminated to hospitals within the UK.

Page number: 31

OPEN ACCESS

Evaluation and management of adult idiopathic intracranial hypertension

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ABSTRACT

This paper summarises the first consensus guidelines for idiopathic intracranial hypertension as an infographic. Following a systematic literature review, a multidisciplinary specialist interest group met and established questions relating to population, interventions, controls and outcomes (PICO). A survey was sent to doctors who manage idiopathic intracranial hypertension (IIH) regularly. Statements were reviewed by national professional bodies, specifically the Association of British Neurologists, British Association for the Study of Headache, the Society of British Neurological Surgeons and the Royal College of Ophthalmologists and by international experts. Key areas are represented based on the guideline, namely: (1) investigation of papilloedema and diagnosis of IIH; (2) management strategies; and (3) investigation and management of acute exacerbation of headache in established IIH. We present an infographic as an aide-mémoire of the first consensus guidelines for IIH.

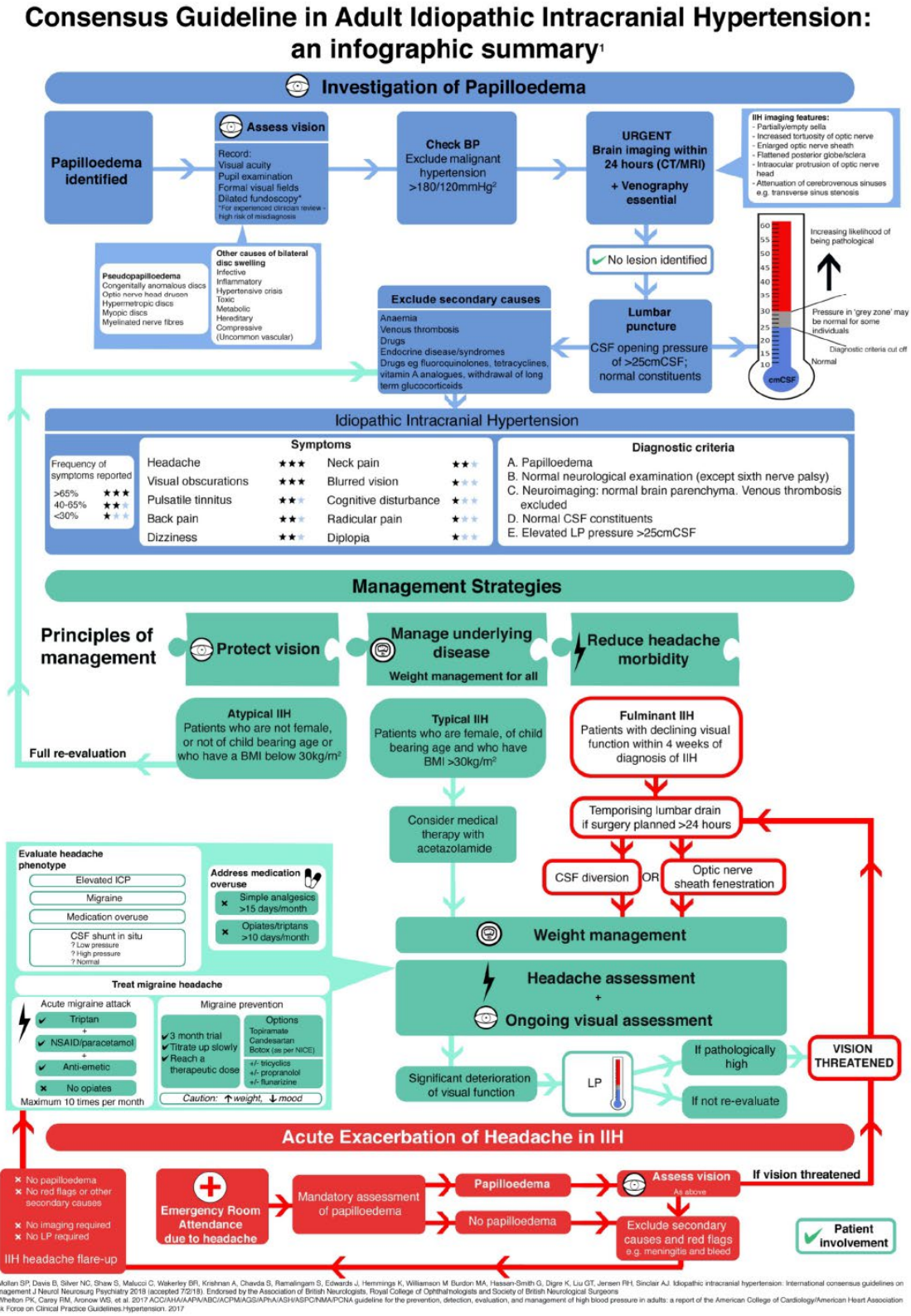
IIH is commonly associated with obesity, younger age and females.[1 2] Patients present acutely to many different specialities and often have multiple acute visits through the course of their disease. The investigation and management of IIH is complex involving many specialities.[3] This infographic summarises three key pathways based on the recommendations of a multidisciplinary, patient-involving and multiprofessional specialist interest group on the investigation and management of IIH.[4]

The basis of the specialist interest group included representation from neurology, neurosurgery, neuroradiology, ophthalmology, nursing, primary care doctors and patient representatives. Questions on PICO were defined and through a large Delphi group exercise; expertise was captured from a wide-reaching group of clinicians, thus reflecting practice from across the UK and internationally. The statements were then critically reviewed by key opinion leaders and by Association of British Neurologists, British Association for the Study of Headache, the Society of British Neurological Surgeons and the Royal College of Ophthalmologists. This is the first consensus guidance for optimal management of IIH.[4]

Identification of papilloedema can be challenging, and clinicians should be aware of the differential diagnosis of pseudopapilloedema (figure 1). Once papilloedema is confirmed, it requires urgent investigations, including lumbar puncture, where the patient experience could be greatly improved.[5] Symptoms of IIH are not pathognomonic, and hence it is essential to apply the diagnostic criteria, including excluding secondary causes, for a definite diagnosis.[4] The lumbar puncture opening pressure was one key area of debate. Within the wider Delphi group, it was clear that there is a 'grey zone' of lumbar puncture opening pressures between 25 cm cerebrospinal fluid (cmCSF) and 30 cmCSF, as to what each expert considered to be pathological, and this is reflected within the infographic thermometer for lumbar puncture opening pressure (figure 1).

Principles of management need to address both the rapidity of the disease that may lead to visual loss in some and require surgical intervention and the morbidity of the headache that can develop in the majority, which substantially affects the quality of life.[6] Weight loss is currently the only established disease-modifying therapy[7] and is notoriously difficult to achieve and maintain.

Evaluation of the headache phenotype is essential to target treatment and to help identify medication-overuse headache. Where there are features of migraine, topiramate may be the first line in treatment,



1. Mollan SP, Davis B, Silver NC, Shaw S, Mallucci C, Wakerley BR, Krishnan A, Chavda S, Ramalingam S, Edwards J, Hemmings K, Williamson M Burdon MA, Hassan-Smith G, Digre K, Liu GT, Jensen RH, Sinclair AJ. Idiopathic intracranial hypertension: International consensus guidelines on management J Neurol Neurosurg Psychiatry 2018 (accepted 7/2/18). Endorsed by the Association of British Neurologists, Royal College of Ophthalmologists and Society of British Neurological Surgeons
2. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.Hypertension. 2017

Figure 1 Consensus Guideline in Adult Idiopathic Intracranial Hypertension: an infographic summary.

and recent evidence indicates that it has a significant intracranial pressure-lowering effect in rodents.[8] Acute exacerbation of headache often leads to reinvestigation with lumbar puncture, and the collective expert opinion reflected that lumbar puncture provides only temporary relief, can lead in some to longer term complications[9] and exacerbation of headache.[10] In those with acute exacerbation of headache, optic nerve examination is essential, and in those found not to have papilloedema, investigation with lumbar puncture and brain imaging is not required, so long as no other secondary causes of headache are suspected. The infographic illustrates the management of acute exacerbation of headache in IIH (figure 1).

Horizon scanning for IIH shows that research is active and that metabolic concepts may potentially provide more understanding of the cause and provide evidence for innovative therapeutic opportunities.[11] A phase 2 randomised control trial with the first novel drug treatment for IIH has finished recruitment[12]; a phase 3 randomised control trial investigating the best method for weight loss is underway[13]; other surgical trials are in planning.

This infographic highlights three areas that are covered by the consensus guideline for adult IIH, which are: (1) investigation of papilloedema and diagnosis of IIH; (2) management strategies; and (3) investigation and management of acute exacerbation of headache in established IIH[4] (figure 1).

Key points

- Cerebral venography is an essential part of the work-up to exclude venous sinus thrombosis as a cause of papilloedema.
- Lumbar puncture opening pressure forms part of the diagnostic criteria; however, most clinicians feel there is a 'grey zone' between 25 cmCSF and 30 cmCSF, which may not be pathological.
- Those with fulminant or precipitous visual decline need urgent surgical treatment, preferably with a ventriculoperintoneal shunt.
- All patients diagnosed with idiopathic intracranial hypertension need sensitive and appropriate discussion regarding weight loss (the only disease-modifying treatment).
- Those with acute exacerbation of headache do not require further neuroimaging or repeat lumbar puncture, unless there are red flag symptoms/signs of infection, or papilloedema with precipitous visual decline.

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Collaborators Brendan Davis (University Hospital North Midlands NHS Trust), Nick Silver (The Walton Centre NHS Foundation Trust), Simon Shaw (University Hospital North Midlands NHS Trust), Conor Mallucci (The Walton Centre NHS Foundation Trust and Alder Hey Children's NHS Foundation Trust), Ben Wakerley (Gloucestershire Hospitals NHS Foundation Trust), Anita Krishnan (The Walton Centre NHS Foundation Trust), Swarup Chavda (University Hospitals Birmingham NHS Foundation Trust), Sateesh Ramalingham (University Hospitals Birmingham NHS Foundation Trust), Julie Edwards (University Hospitals Birmingham NHS Foundation Trust and Sandwell and West Birmingham NHS Trust), Krystal Hemmings (IIH UK Charity), Shelly Williamson (IIH UK Charity), Mike Burdon (University Hospitals Birmingham NHS Foundation Trust), Ghaniah Hassan-Smith (University of Birmingham), Kathleen Digre (Moran Eye Center, University of Utah) Grant Liu (Children's Hospital of Philadelphia and Hospital of the University of Pennsylvania), Rigmor Jensen (Danish Headache Centre, Copenhagen), Jane Anderson, (Cambridge University Hospitals NHS Foundation Trust), Peter Goadsby (King's College Hospital), Tim Matthews (University Hospitals Birmingham NHS Foundation Trust) and Jan Hoffman (University Medical Centre Hamburg).

Contributors SPM and AJS drafted the infogram. CH executed the drawing of the infogram. SPM wrote the initial draft. JM and AJS critically reviewed the paper and infogram.

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Competing interests None declared.

Patient consent Not required.

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Publication 4: What are the research priorities for idiopathic intracranial hypertension?

Manuscript title:
Mollan S, Hemmings K, Herd CP, Denton A, Williamson S, Sinclair AJ. What are the research priorities for idiopathic intracranial hypertension? A priority setting partnership between patients and healthcare professionals. BMJ Open. 2019;9(3):e026573

Involvement:
I performed a literature review. I helped construct the surveys. I ensured wide dissemination and a social media program to ensure the surveys were taken up. I helped refine uncertainties, sorting of the replies into categories and identifying those out of scope and removing questions that could not be answered. I worked on the interim prioritisation, where a final list of 26 prioritised questions were taken forward to the final workshop. I helped construct the second survey. I arranged the venue for the final workshop. I took part in the day long of workshop to distil the priorities and rank them into the top 10. I wrote the initial manuscript and made the revisions.

Page number: 32

BMJ Open

What are the research priorities for idiopathic intracranial hypertension? A priority setting partnership between patients and healthcare professionals

Susan Mollan,[1] Krystal Hemmings,[2] Clare P Herd,[3] Amanda Denton,[2] Shelley Williamson,[4] Alexandra J Sinclair[5,6]

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SM and KH contributed equally.

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ABSTRACT

Objective Idiopathic intracranial hypertension (IIH) is under-researched and the aim was to determine the top 10 research priorities for this disease.

Design A modified nominal group technique was used to engage participants who had experience of IIH.

Setting This James Lind Alliance Priority Setting Partnership was commissioned by IIH UK, a charity.

Participants People with IIH, carers, family and friends, and healthcare professionals participated in two rounds of surveys to identify unique research questions unanswered by current evidence. The most popular 26 uncertainties were presented to stakeholders who then agreed the top 10 topics.

Results The top 10 research priorities for IIH included aetiology of IIH, the pathological mechanisms of headache in IIH, new treatments in IIH, the difference between acute and gradual visual loss, the best ways to monitor visual function, biomarkers of the disease, hormonal causes of IIH, drug therapies for the treatment of headache, weight loss and its role in IIH and finally, the best intervention to treat IIH and when should surgery be performed.

Conclusions This priority setting encouraged people with direct experience of IIH to collectively identify critical gaps in the existing evidence. The overarching research aspiration was to understand the aetiology and management of IIH.

Strengths and limitations of this study

- This is the first collaboration of patients, carers and clinicians with experience of idiopathic intracranial hypertension (IIH) to achieve consensus on the priorities for future research.
- The James Lind Alliance (JLA) methods are patient centred and give funding bodies an unbiased agenda for research in IIH.
- Using online surveys as the main method for gathering questions for this Priority Setting Partnership (PSP) may mean that not all those with experience of IIH were aware or able to participate in the process.
- It is conceivable that possibly all the research questions gathered are not exhaustive.
- While the JLA process and IIH PSP study recommend those research priorities that are important, there is no guarantee of research funding.

INTRODUCTION

Clinical uncertainty in idiopathic intracranial hypertension (IIH) is evident, with the first consensus guidelines for investigation and management stating uncertainties in every aspect of the disease.[1] The 2015 Cochrane review concluded that there is a lack of evidence to guide pharmacological treatment.[2] There are a few published randomised clinical trials[3 4] and a small number of ongoing trials.[5 6] Research is infrequent due to the rarity of the IIH[7 8] and the lack of understanding of the underlying pathology.[9]

IIH predominantly affects overweight women of childbearing age with the incidence of the disease documented to be rising[10] with the increasing prevalence of obesity.[7 8] In those with severely affected vision, surgery may be indicated.[1] For the majority, it can be a chronic condition, with headaches impacting on the quality of life of patients,[11] and an economic burden.[10 12]

Understanding where research should be directed was a priority for IIH UK, the leading charity for IIH in the UK. The James Lind Alliance (JLA), a UK National Institute for Health Research-supported initiative, aims to provide a transparent process that enables patients and healthcare professionals (HCP) to work together to agree on the most important uncertainties to inform the research agenda. The aim of this IIH Priority Setting Partnership (PSP) was to identify gaps in knowledge that matter most to key stakeholders (patients, carers and clinicians), and to indicate where future funding should be placed.

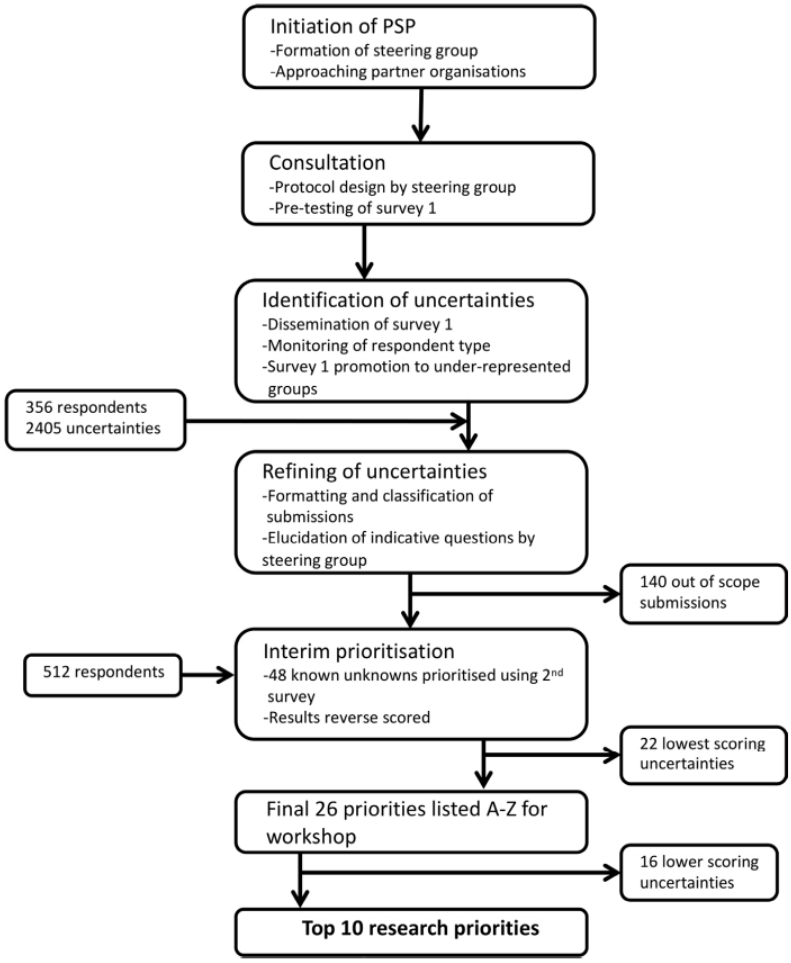

Figure 1 Consort diagram and details of the JLA IIH PSP. IIH, idiopathic intracranial hypertension; JLA, James Lind Alliance; PSP, Priority Setting Partnership.

METHODS

IIH PSP process

The University of Birmingham, UK, acted as an academic partner to the IIH PSP and the process was led by the IIH UK research representative, in collaboration with the JLA (www.jla.nihr.ac.uk). A steering group with representation from IIH UK, patients and all the major specialities associated with IIH plus an independent information specialist oversaw the process (online supplementary table 1). In February 2017, key organisations accepted the invitation to become partners. They included Association of British Neurologists, British Association for the Study of Headache, British and Irish Orthoptic Society, Fight for Sight, The Royal College of Ophthalmologists, Society of British Neurological Surgeons cerebrospinal fluid (CSF) group, Shine, Neurological Alliance and The United Kingdom Neuro-Ophthalmology Special Interest Group (online supplementary table 2). The PSP stages were broadly based on the four-step process developed by the JLA (figure 1).[13]

This PSP was concerned with adult IIH only and any responses exclusively relating to children were excluded. There was limited funding for the project, and including the paediatric population would have required funding for two different work streams. It is well documented the expectantly different phenotype between adult and those prepubescent children with IIH.[14] However, responses were not limited by those who submitted and hence, those with children with IIH are likely to be included. Indeed, at the final stakeholder meeting, there was representation from carers of children with IIH. Responses concerning the classification of the disease, healthcare funding/entitlements or statements without a discernible question were excluded.

The prioritisation survey questions were constructed (online supplementary table 2) by the steering group, aided by the first guidelines in IIH where uncertainties exist around the diagnosis, investigation and management.[1] This first survey was advertised by partners (online supplementary table 3), IIH UK and steering

Figure 2 Final top 10 ranked uncertainties for concerning the treatment and management of people with idiopathic intracranial hypertension (IIH).

group members. All responses were refined to understandable 'uncertainties' with the exception of those considered to be 'out of scope'. These were categorised using the UK Clinical Research Collaboration Health Research Classification System, sorted into themes and then formulated into indicative questions by steering group members, working in groups with at least one HCP and one patient representative. A literature search was conducted with the electronic databases, CENTRAL, Embase and MEDLINE, searched from inception to March 2018 for systematic reviews using strategies based on those used by Piper *et al*.[2] The 'known knowns' with reference to the appropriate literature and duplicate questions were removed. Questions were amalgamated when practical to do so. The long list was then verified by the PSP lead and discussions were held with the wider steering group if disagreements occurred.

The known unknowns were then used for the interim survey. Respondents ranked the questions, returning their top 10. The rankings were reverse scored and the total scores for the two groups, individuals with IIH, friends or carers, and HCP, were calculated separately to ensure an equal weighting. The most popular 26 questions were then taken forward, which included the top 10 for both groups, to the final workshop, with the aim of consensus on the top 10 priorities.[13] Data relating to the PSP are available on reasonable request to IIH UK (www.iih.org.uk).

Patient and public involvement

This research priority partnership was established by IIH UK, a charity that is run by carers and people with IIH. At each stage of the JLA process, patients and carers were equal collaborators in the design and decisions including the survey design and piloting, survey participation and the final workshop. They disseminated the surveys on the charity website and via social media. All participants were able to indicate a desire for further involvement and information about the results.

RESULTS

The prioritisation survey generated 356 responses (figure 1). Demographic data for those with IIH is provided in online supplementary table 4 and details of HCP specialisms in online supplementary table 5. Of the 2405 generated uncertainties, 140 were out of scope. The resulting 2265 were grouped into 64 indicative questions. Sixteen were deemed to be already known or unanswerable by research, leaving 48 questions for presentation in the interim survey. Responses from 512 people were collected in a ratio of 4:1 people with IIH, friends and carers to HCP.

A final list of 26 prioritised questions was generated from the analysis of the interim survey, which included the top 10 for both groups (online supplementary table 6). The most common themes from non-HPC (healthcare professional) were why the disease develops and progresses, hormonal causes and female predominance and the conditions associated with IIH. For HCP education, the utility of biomarkers and biological mechanisms of headache were the most common. At the consensus workshop, the top 10 priorities were agreed (figure 2; online supplementary table 7).

DISCUSSION

Understanding the most relevant research projects to fund can be challenging. It is imperative that the topics identified in a disease area have the utmost relevance to patients affected by the disease and recognised by clinicians that have a clear understanding of the clinical entity. We have undertaken a JLA PSP to establish the top 10 research areas for IIH.

The IIH JLA PSP was funded by IIH UK and set up those who have an active collaboration to improve care for people with IIH.[15] The principles and structured process outlined by the JLA was adhered to steadfastly throughout.[13] All data was maintained in a manner that could be tracked back at any point to the original questions and demographic source; this provided transparency.

A major challenge for the IIH PSP steering group was to engage all the relevant HCP (namely, neurologists,

ophthalmologists, neurosurgeons, radiologists and orthoptists). The speciality diversity brought strength to the process and allowed for a broad inclusion; however, during the final selection for the top 10, clinicians were clearly polarised by their individual specialism. There are a number of surgical treatments for fulminant visual loss in the form of CSF diversion, as directed by neurosurgeons, and optic nerve sheath fenestration, as performed by ophthalmic surgeons.[16] More recently, interventional radiologists have performed venous sinus stenting for IIH.[17] Physicians (both neurologists and ophthalmologists) use weight loss and medical therapies, such as acetazolamide and topiramate.[1 18] This mix of specialism and approach in certain patient groups, that is those at threat of visual loss or with chronic headache, led to expectantly different opinions; for example, surgeons were keen for novel interventions, whereas physicians were promoting better medical therapies.

At the interim survey, it was clear that there was a discrepancy between the non-HCP and HCP in their most popular themes, with patients keen for research into the aetiology, and HCP more commonly ranked education, biomarkers and pathological mechanisms driving headache. The top priority of the patients' group at the interim survey was the same as the final result of the consensus workshop.

Some differing opinions between non-HCP and HCP were expressed at the workshop. One issue was surrounding weight loss, seen by physicians as the only disease modifiable therapy and so a high priority for further understanding. This was a highly sensitive issue among the patients and carers present who voiced that it was not considered so important by patients. During the workshop, a collective decision was made to have a wide scope within the top 10 areas. If a topic was already featured high within the list, questions that contained a similar theme were purposely voted lower. For example, weight loss, the longer more detailed question was ranked higher than the question regarding bariatric surgery, with the reasoning that it could be answered not only by the weight loss question but also by number 10, the intervention question. For this reason, no further ranking below the top 10 should be published. Of note, two areas that did not feature in the top 10, namely, multidisciplinary clinics and an education programme. They were scored as important during the interim survey, particularly by HPC. The consensus workshop delegates agreed that although these are highly important, the PSP is intended to inform grant bodies who fund research and these areas were universally accepted to require improvement.

Strengths

Within the feedback, people with IIH voiced that they felt their opinions were often not heard; therefore, the IIH PSP has allowed them a voice. There was a good response rate from all groups when considering how rare IIH is. Submissions with low duplication rates were not removed, a process which can introduce bias. All submitted uncertainties were considered in the long list if they were determined to be known unknowns, including those asked by a single respondent. The data analysis followed standard protocols, though it was complicated by the use of multiple questions in the initial survey (online supplementary table 3) as each respondent could appear in up to seven separate initial categories.

Limitations

Despite the use of identification codes, the multi-level process meant that the number of individuals contributing to the final data set could not be reasonably calculated. The project took 18 months and surveys were closed on schedule, leaving the possibility that this happened before the maximum number of respondents could contribute. Using online surveys as the main method for gathering questions for this PSP may mean that not all those with experience of IIH were aware or able to participate in the process. It is conceivable that possibly all the research questions gathered are not exhaustive. While the JLA process and IIH PSP study recommend those research priorities that are important, there is no guarantee of research funding.

CONCLUSIONS

The IIH PSP has been an opportunity to understand the areas that are important to all. The primary topic of underlying aetiology requires work both clinically and within the basic laboratory research. Another key area highlighted by this PSP is that of mechanisms of headache in IIH. There is increasing evidence regarding the phenotype of the IIH headache, which is a challenging tradition regarding the raised intracranial pressure (ICP) headache.[19 20] Future work should explore novel therapies for headache in IIH, which is the key driver in lowering the quality of life in this patient cohort.[11] The PSP has the potential to influence the research agenda and consequently in time all area of management, from medical to surgical interventions for this currently idiopathic disease.

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Correction notice This article has been corrected since it was published online. The license type has been updated from CC BY-NC to CC BY.

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Contributors SM: interpretation of the survey results and drafting and review of the manuscript. KH: PSP patient lead, administration of both surveys and drafting and review of the manuscript. CPH: literature review, independent information specialist and drafting and review of the manuscript. AD: critical review of the manuscript. SW: organisation of the consensus final workshop and critical review of the manuscript. AJS: PSP clinical lead, interpretation of the survey results and critical review of the manuscript. All authors were steering group members and have read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The IIH UK internal review board formally reviewed the project and further ethical approval was not required. All data were anonymised and sent to the information specialist at the University of Birmingham for processing.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Any unpublished data are available from the James Lind Alliance website and from the authors.

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Supplemental Table 1: The steering group members and their role

Person	Role
Krystal Hemmings	IIH UK Research representative and PSP patient led
Alex Sinclair	Clinical lead and neurologist
Michelle Williamson	IIH UK Chair trustee, project coordinator and carer
Clare Herd	Information specialist
Martin Plowright	IIH patient
Norma-Ann Dan	IIH UK patient representative
Amanda Denton	IIH UK patient representative
Rachel Bennett	IIH patient
Jayne Best	Neuro-Ophthalmologist
Arun Chandran	Neuro-radiologist
Julie Edwards	Headache nurse specialist
Anita Krishnan	Neurologist
Kamal Mahawar	Bariatric surgeon
Susan Mollan	Neuro-Ophthalmologist
Caroline Rick	Trial methodologist
Ahmed Toma	Neurosurgeon

Supplemental Table 2: The prioritisation survey was designed using Qualtrics software (www.qualtrics.com) and responses were requested to the following seven questions:

1. What questions do you have about how the diagnosis of IIH is made?

2. What questions do you have about why people get IIH?

3. What questions do you have about the management of vision in IIH?

4. What questions do you have about the management of headache in IIH?

5. What questions do you have about weight management in IIH?

6. What questions do you have about care provision for patients with IIH?
(e.g. General Practice, inpatient, outpatient care)

7. Do you have any other questions about IIH that you feel are important
but do not fall into the categories above?

Supplemental Table 3: Partner organisations in alphabetical order

ABN- Association of British Neurologists
BASH - British Association for the Study of Headache
BIOS - British and Irish Orthoptic Society
Fight for Sight – _The Eye Research Charity
RCOphth – _The Royal College of Ophthalmologists
SBNS CSF subgroup - The Society of British Neurological Surgeons
Shine – _Spina bifida, Hydrocephalus, Information, Networking, Equality
The Neurological Alliance
UKNOSIG - The United Kingdom Neuro-Ophthalmology Special Interest Group

Supplementary Table 4: Characteristics of participants with IIH of first survey

Number	180
Female (%)	96
Median age (years)	35
Ethnicity (%)	
White	92
Black or Asian	3
Multiple ethnic backgrounds	4
Not stated	1

Supplementary Table 5: Declared specialism of the healthcare professionals in first survey

Declared specialism of the healthcare professional	**% of respondents**
Neurologist	45
Ophthalmologist	11
Neurosurgeon	10
Neuro-Ophthalmologist	9
Other	8
Trainee	6
Bariatric Surgeon	3
General Practitioner	3
Nurse	2
Neuroradiologist	1
Orthoptist	1
Not declared	1

Supplemental Table 6: 26 Questions for IIH PSP final workshop in alphabetical order

Are multidisciplinary clinics (joint clinics of neurology, ophthalmology, neurosurgery, dietetics and specialist nurses etc.) clinically and cost effective for the management of IIH and would they improve patient experience?
Are non-invasive intracranial pressure (ICP) measurements accurate and clinically useful?
Can IIH biomarkers (tests in body fluids for example urine, saliva, blood, or brain scans) help diagnosis, predict the risk and guide therapy decisions in IIH?
Can novel therapies for IIH be developed which are effective, safe, and tolerable and potentially help with weight loss as well as reducing brain pressure?
Do lumbar punctures (LPs) have long-term safety complications?
Do the benefits of the drug treatments for IIH outweigh the side effects?
How big is the impact of headache in IIH (how severe are headaches, how often do they occur, how many years do they continue for and how do they impact patients quality of life)?
Is bariatric surgery effective in IIH and at what point in the disease should it be performed?
Is cerebral venous stenosis the cause or consequence of IIH?
Is IIH a lifelong condition?
Is IIH caused by increased production or lack of cerebral spinal fluid (CSF) absorption?
Is there a genetic cause of IIH?
Is there a single or are there multiple causes for IIH?
What are the best ways to monitor visual function?
What are the biological mechanisms of headache in IIH and why in some do headaches continue even after papilloedema has resolved?
What are the hormonal causes for IIH and why is IIH primarily associated with female gender?
What are the triggers for periods of high intracranial pressure (ICP) in people with IIH?
What is happening in the body of a person with IIH which causes the development of the disease, the symptoms and the progression of the disease?
What is the biological explanation for the differences between rapid visual loss compared with gradual visual loss in IIH and how can this be predicted?
What medications are effective and safe to treat IIH headaches?
What other conditions / features are associated with IIH (e.g. depression, sleep apnoea, endocrine disorders, cognition, nerve pain)?
Which is the best type of surgery to treat IIH and when should surgery be performed?
Why do people get IIH without papilloedema (IIHWOP) and how should this be treated?
Why is obesity a risk factor for IIH in women and why is this not the case in men?
With regard to weight loss in IIH: how much is needed to treat IIH and how quickly does it work? What is the best, safest and most acceptable method to achieve this in the short and long term? Additionally, does the initial Body Mass Index (BMI) of the patient have an effect?
Would an education program for health care professionals and patients with IIH improve care and disease experience for IIH patients

Supplemental Table 7: Final Top 10 ranked uncertainties for the concerning the treatment and management of people with Idiopathic Intracranial Hypertension

Ranking	Research priority
1	In the individual with IIH; what causes the disease, the symptoms and the progression of the disease?
2	What are the biological mechanisms of headache in IIH and why in some do headaches continue even after papilloedema has resolved?
3	Can new medical therapies for IIH be developed which are effective, safe, and tolerable and potentially help with weight loss as well as reducing brain pressure?
4	What is the biological explanation for the differences between rapid visual loss compared with gradual visual loss in IIH and how can this be predicted?
5	What are the best ways to monitor visual function?
6	Can IIH biomarkers (tests in body fluids for example urine, saliva, blood, or brain scans) help diagnosis, predict the risk and guide therapy decisions in IIH?
7	What are the hormonal causes for IIH and why is IIH primarily associated with female sex?
8	What medications are effective and safe to treat IIH headaches?
9	With regard to weight loss in IIH: how much is needed to treat IIH and how quickly does it work? What is the best, safest and most acceptable method to achieve this in the short and long term? Additionally, does the initial Body Mass Index (BMI) of the patient have an effect?
10	Which is the best type of intervention to treat IIH and when should surgery be performed

Publication 5: Bariatric surgery versus community weight management intervention for treatment of idiopathic intracranial hypertension (IIH:WT): a randomised controlled trial

Manuscript title:
Mollan SP, Mitchell JL, Ottridge RS, Aguiar M, Yiangou A, Alimajstorovic Z, Cartwright D, Scotton W, Wakerley B, Matthews TD, Anson A, Hickman S, Benzimra J, Rick C, Singhal R, Tahrani AA, Brick, Frew E, Sinclair AJ. Bariatric surgery versus community weight management intervention for treatment of idiopathic intracranial hypertension (IIH:WT): a randomised controlled trial. JAMA Neurol. 2021;78(6):678-686.

Involvement:
I recruited patients to the trial. I advised on Ophthalmology aspects of the protocol. I performed part of patient visits. I supervised other clinical research fellows in acquiring trial data. I ensured timely follow-up of those requiring escalation of care during the trial. I helped interpret the analysis. I wrote the initial draft of the publication. I revised the publication following critical internal and external review.

I disseminated the results at the Oxford Ophthalmological Congress July 2022, winning the Ian Fraser Cup for clinical research.

I contacted the NICE obesity guideline group and lobbied for IIH to be included as an obesity related co-morbidity.

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Effectiveness of Bariatric Surgery vs Community Weight Management Intervention for the Treatment of Idiopathic Intracranial Hypertension
A Randomized Clinical Trial

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IMPORTANCE Idiopathic intracranial hypertension (IIH) causes headaches, vision loss, and reduced quality of life. Sustained weight loss among patients with IIH is necessary to modify the disease and prevent relapse.

OBJECTIVE To compare the effectiveness of bariatric surgery with that of a community weight management (CWM) intervention for the treatment of patients with active IIH.

DESIGN, SETTING, AND PARTICIPANTS This 5-year randomized clinical trial (Idiopathic Intracranial Hypertension Weight Trial) enrolled women with active IIH and a body mass index (calculated as weight in kilograms divided by height in meters squared) of 35 or higher at 5 National Health Service hospitals in the UK between March 1, 2014, and May 25, 2017. Of 74 women assessed for eligibility, 6 did not meet study criteria and 2 declined to participate; 66 women were randomized. Data were analyzed from November 1, 2018, to May 14, 2020.

INTERVENTIONS Bariatric surgery (n = 33) or CWM intervention (Weight Watchers) (n = 33).

MAIN OUTCOMES AND MEASURES The primary outcome was change in intracranial pressure measured by lumbar puncture opening pressure at 12 months, as assessed in an intention-to-treat analysis. Secondary outcomes included lumbar puncture opening pressure at 24 months as well as visual acuity, contrast sensitivity, perimetric mean deviation, and quality of life (measured by the 36-item Short Form Health Survey) at 12 and 24 months. Because the difference in continuous outcomes between groups is presented, the null effect was at 0.

RESULTS Of the 66 female participants (mean [SD] age, 32.0 [7.8] years), 64 (97.0%) remained in the clinical trial at 12 months and 54 women (81.8%) were included in the primary outcome analysis. Intracranial pressure was significantly lower in the bariatric surgery arm at 12 months (adjusted mean [SE] difference, −6.0 [1.8] cm cerebrospinal fluid [CSF]; 95% CI, −9.5 to −2.4 cm CSF; $P = .001$) and at 24 months (adjusted mean [SE] difference, −8.2 [2.0] cm CSF; 95% CI, −12.2 to −4.2 cm CSF; $P < .001$) compared with the CWM arm. In the per protocol analysis, intracranial pressure was significantly lower in the bariatric surgery arm at 12 months (adjusted mean [SE] difference, −7.2 [1.8] cm CSF; 95% CI, −10.6 to −3.7 cm CSF; $P < .001$) and at 24 months (adjusted mean [SE] difference, −8.7 [2.0] cm CSF; 95% CI, −12.7 to −4.8 cm CSF; $P < .001$). Weight was significantly lower in the bariatric surgery arm at 12 months (adjusted mean [SE] difference, −21.4 [5.4] kg; 95% CI, −32.1 to −10.7 kg; $P < .001$) and at 24 months (adjusted mean [SE] difference, −26.6 [5.6] kg; 95% CI, −37.5 to −15.7 kg; $P < .001$). Quality of life was significantly improved at 12 months (adjusted mean [SE] difference, 7.3 [3.6]; 95% CI, 0.2-14.4; $P = .04$) and 24 months (adjusted mean [SE] difference, 10.4 [3.8]; 95% CI, 3.0-17.9; $P = .006$) in the bariatric surgery arm.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, bariatric surgery was superior to a CWM intervention in lowering intracranial pressure. The continued improvement over the course of 2 years shows the impact of this intervention with regard to sustained disease remission.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02124486

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Idiopathic intracranial hypertension (IIH) is a debilitating condition characterized by increased intracranial pressure (ICP) that causes optic disc swelling known as papilledema, with a risk of permanent visual loss and chronic headaches that lead to reduced quality of life.[1,2] The condition predominately affects women aged 25 to 36 years, with weight gain being a major risk factor.[3-5]

The incidence of IIH is increasing and has been associated with increasing obesity rates worldwide.[3,4] Modest weight gain (approximately 5%) has been associated with an increased risk of developing IIH and experiencing relapses of the disease.[5] Weight loss has been reported to be a beneficial treatment strategy, with a reduction in body weight of 3% to 15% associated with disease remission as defined by ICP normalization and papilledema resolution.[6] Body weight is the main modifiable factor associated with the development of IIH,[7] and a patient-physician priority partnership has emphasized the importance of conducting research to evaluate the most effective approach to treating patients with IIH through weight loss interventions.[8]

Community weight management interventions (excluding very low-energy diets) have been associated with modest weight loss (approximately 5%).[9] A previous study[6] reported that a very low-energy diet (≤425 kcal per day) for 3 months was associated with weight loss of 15%, reductions in ICP, improvements in papilledema and visual function, and decreases in headache frequency and severity, with concomitant reductions in the use of analgesic medications. Maintaining weight loss is difficult, and most patients regain weight over a 2- to 5-year period.[10] Bariatric surgery has been associated with sustained long-term weight loss (25%-30%) as well as positive cardiovascular and metabolic outcomes.[11,12] Case series suggest that bariatric surgery is also associated with remission among patients with IIH, with concomitant improvement in symptoms and discontinuation of medication, but to our knowledge, there is currently no evidence from randomized clinical trials.[13,14]

We hypothesized that bariatric surgery would be superior to a community weight management intervention in reducing ICP among patients with IIH because of greater sustained weight loss. We therefore conducted a multicenter randomized clinical trial (Idiopathic Intracranial Hypertension Weight Trial [IIH:WT]) comparing bariatric surgery with a community weight management intervention to evaluate which approach was more effective in decreasing ICP among participants with active IIH, with the primary end point being lumbar puncture (LP) opening pressure measured after 12 months.

Key Points

Question Is bariatric surgery superior to a community weight management intervention in sustaining the weight loss necessary to achieve sustained remission among patients with idiopathic intracranial hypertension?

Findings In this randomized clinical trial of 66 women with idiopathic intracranial hypertension and a body mass index of 35 or higher, bariatric surgery was superior to a community weight management intervention in decreasing intracranial pressure, with continued improvement at 2 years.

Meaning The study's findings indicate that, among women with idiopathic intracranial hypertension and a body mass index of 35 or higher, bariatric surgery is an effective treatment to reduce intracranial pressure and for sustained disease remission.

Methods

Trial Design and Participants

The IIH:WT was a 5-year multicenter parallel-group randomized clinical trial (NCT02124486) (trial protocol in Supplement 1). We recruited participants at 5 National Health Service hospitals in the UK between March 1, 2014, and May 25, 2017. Participants were identified from the neurology and ophthalmology clinics of 7 National Health Service hospitals (eMethods 1 in Supplement 2). The National Research Ethics Committee of West Midlands approved the clinical trial, and the trial protocol was reported before enrollment was completed.[15] All participants provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials.

Participants

We recruited women aged 18 to 55 years who met the diagnostic criteria for IIH[16]; had normal results from brain imaging, including magnetic resonance venography or computed tomographic venography (apart from radiological signs of increased ICP); had a body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 35 or higher; and had not succeeded in losing weight or maintaining weight loss. To be classified as having active disease, participants were required to have a baseline LP opening pressure of 25 cm cerebrospinal fluid (CSF) or higher and to have papilledema at baseline. Detailed inclusion and exclusion criteria are provided in eTable 1 in Supplement 2.

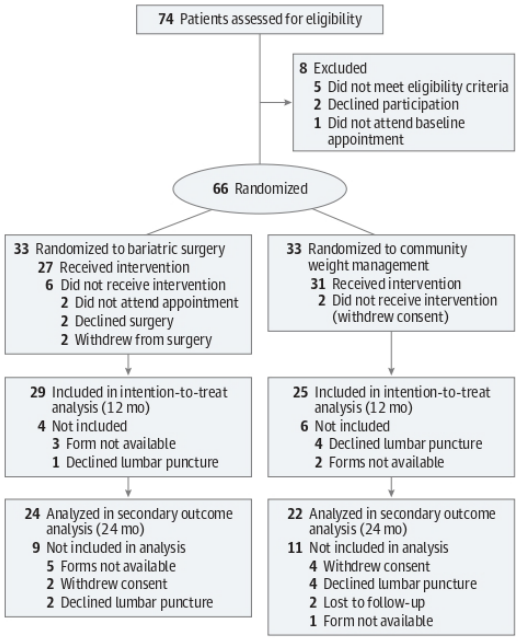
Randomization and Treatment

Participants were randomized in a 1:1 ratio to receive either a community weight management intervention (Weight Watchers; weight management arm) or bariatric surgery (surgery arm) using computer-generated random numbers and were stratified by use vs nonuse of acetazolamide medication (eMethods 2 in Supplement 2). All assessors were masked to treatment allocation. A complete medical history, clinical measurements, and a headache diary were completed by all participants in accordance with the study protocol (Supplement 1).[15]

Outcome Measures

The primary outcome was the difference in ICP between the surgery arm and the weight management arm as measured by LP opening pressure at 12 months. Secondary outcomes included LP opening pressure at 24 months, visual acuity (logMAR; measured using Early Treatment Diabetic Retinopathy Study testing charts), contrast sensitivity (assessed using the

Figure 1. CONSORT Diagram



In the bariatric surgery arm, 18 patients were assessed 2 weeks after surgery.

Mars Letter Contrast Sensitivity Test), perimetric mean deviation (central threshold automated perimetry measured using the Humphrey 24-2 Swedish interactive thresholding algorithm), and health-associated quality of life (measured using the 36-item Short Form Health Survey,[17] the Hospital Anxiety and Depression Scale,[18] and the 5-level EuroQol 5-Dimension questionnaire[14]). Evaluations were performed at baseline and at 3, 6, 12, and 24 months and were planned for 60 months.

Optic nerve head swelling was assessed using spectral domain optical coherence tomography (Spectralis; Heidelberg Engineering). Three neuroophthalmologists (J.B., T.D.M., and S.P.M.) who were masked to participant identity graded papilledema from color fundus photographs (Topcon Medical) using Frisén classification.[19] Headache symptoms were evaluated using the 6-item Headache Impact Test,[20] symptom severity scores (rating scale, 0 to 10, with 0 indicating no pain and 10 indicating maximum pain), symptom frequency (days per month), and analgesic medication use (days per month). Any adverse events or serious adverse events (SAEs) that occurred were documented.

Sample Size Calculation

In a previous study of weight loss among patients with IIH who followed a low-energy diet for 3 months, LP opening pressure was found to be significantly reduced by a mean (SD) of 8 (4.2) cm CSF ($P < .001$), with mean (SD) weight loss of 15.3% (7.0%) of body weight.[6] We inferred that a similar reduction of LP opening pressure of 8 cm CSF would occur in the surgery arm and that a smaller reduction of 3 cm CSF would occur in the weight management arm (a value to reflect changes slightly greater than the baseline fluctuations observed in the previous study[6]).

We therefore planned to detect a mean difference of 5.0 cm CSF between the groups with 90% power and an error rate of $\alpha = .05$ using a 2-sided t test (assuming an SD of 5.1 cm CSF),[15] which would have required a sample of 46 patients (23 patients per arm). To allow for a 28% withdrawal rate, 32 participants per arm were required. Based on these assumptions, 66 women (33 participants per arm) were recruited.

Statistical Analysis

All primary analyses (primary and secondary outcomes, including safety outcomes) were evaluated using intention-to-treat analysis. A per protocol analysis was also performed for the primary outcome as part of a planned secondary analysis. For the per protocol analysis, the surgery arm was defined as participants who had undergone bariatric surgery within 12 months of randomization, and the weight management arm was defined as participants who had not undergone bariatric surgery within 12 months of randomization. Analysis was completed using received data only, with effort made to follow up with participants even after instances of protocol nonadherence to minimize the potential for bias. No imputation of missing data was conducted. The analysis of visual data included data from both eyes, with data on the more affected eye at baseline (defined by perimetric mean deviation) being reported.

Statistical analysis was performed using R software, version 3.6.3 (R Foundation for Statistical Computing). Data were reported as means, SDs or SEs (with medians and interquartile ranges [IQRs] used for nonnormal data), and 95% CIs, as appropriate. Hierarchical linear regression models were used to analyze repeated measures of the primary and secondary outcomes and to estimate differences adjusted for baseline values (eMethods 2 and eTable 2 in Supplement 2). In these models, population-level effects (ie, fixed effects) included the intercept, time (as a factor variable), and the 2-way interaction of treatment arm and time (as a factor variable) to model differences in treatment effects over time. Group-level effects (ie, random effects) comprised patient-level adjustments to the intercept. Because the difference in continuous outcomes between groups is presented, the null effect was at 0. The threshold for statistical significance was prespecified at $P = .05$. Data were analyzed from November 1, 2018, to May 14, 2020.

Results

Participants

Between 2014 and 2017, 74 women were assessed for eligibility; 6 women did not meet study criteria, and 2 women declined to participate. A total of 66 women (mean [SD] age, 32.0 [7.8] years) enrolled in the study and were randomly assigned to either the surgery arm (n = 33) or the weight management arm (n = 33) (**Figure 1**). The study population had a mean (SD) LP opening pressure of 35.5 (7.0) cm CSF, and the clinical trial arms were balanced with regard to baseline characteristics (**Table 1**).

Table 1. Baseline Characteristics of Participants in the Trial

Characteristic	Participants[a]		
	All (N = 66)	Bariatric surgery arm (n = 33)	CWM intervention arm (n = 33)
Age, mean (SD), y	32.0 (7.8)	31.0 (8.0)	33.0 (7.7)
Female	66 (100)	33 (100)	33 (100)
Race/ethnicity			
White	55 (83.3)	27 (81.8)	28 (84.8)
Mixed or multiple	5 (7.6)	3 (9.1)	2 (6.1)
Black, African, or Caribbean	5 (7.6)	3 (9.1)	2 (6.1)
Asian or British Asian	1 (1.5)	0	1 (3.0)
Duration of IIH diagnosis, median (range), y	1.1 (0.5-2.6)	1.1 (0.6-2.7)	0.8 (0.4-2.5)
Frisén grade of worse eye, mean (SD)	2.1 (1.0)	2.0 (0.9)	2.2 (1.1)
Perimetric mean deviation of worse eye			
Mean (SD), dB	−3.6 (3.7)	−3.6 (3.5)	−3.5 (3.8)
Participants, No.	65	32	33
LP opening pressure at diagnosis			
Mean (SD), cm CSF	35.5 (7.0)	34.5 (5.7)	36.5 (8.0)
Participants, No.	60	30	30
LP opening pressure at baseline, mean (SD), cm CSF	34.7 (5.7)	34.8 (5.8)	34.6 (5.6)
Acetazolamide receipt	19 (28.8)	8 (24.2)	11 (33.3)

Abbreviations: CSF, cerebrospinal fluid; CWM, community weight management; IIH, idiopathic intracranial hypertension; LP, lumbar puncture.

[a] Data are presented as number (percentage) of participants unless otherwise indicated.

Adherence to Protocol

A total of 64 women (97.0%) remained in the clinical trial at 12 months, and 54 women (81.8%) completed the primary outcome. Six participants in the surgery arm did not receive bariatric surgery based on personal choice, and no participants were medically declined for surgery. Two participants withdrew from the weight management arm; between 12 and 24 months, 2 additional participants in the weight management arm underwent bariatric surgery (on a self-funded basis) (Figure 1).

Treatments

In the surgery arm, the median time from randomization to bariatric surgery was 4.4 months (range, 2.2-10.3 months). Among the 27 participants who underwent surgery, the predominant procedure was Roux-en-Y gastric bypass (12 participants [44.4%]) followed by gastric banding (10 participants [37.0%]) and laparoscopic sleeve gastrectomy (5 participants [18.5%]). Among those in the weight management arm, the mean (SD) number of Weight Watchers face-to-face sessions attended was 14.3 (10.6), with 19 of 33 participants (57.6%) attending at least 1 session.

Primary Outcomes

The mean (SD) LP opening pressure decreased from 34.8 (5.8) cm CSF at baseline to 26.4 (8.7) cm CSF at 12 months (adjusted mean [SE] difference, −8.7 [1.3] cm CSF; 95% CI, −11.3 to −6.1 cm CSF; $P < .001$) in the surgery arm and from 34.6 (5.6) cm CSF at baseline to 32.0 (5.2) cm CSF at 12 months (adjusted mean [SE] difference, −2.5 [1.4] cm CSF; 95% CI, −5.2 to 0.3 cm CSF; $P = .08$) in the weight management arm, but the difference for the latter was not significant (**Table 2** and **Figure 2**). The prespecified primary outcome analysis indicated that the adjusted mean (SE) difference in LP opening pressure was −6.0 (1.8) cm CSF (95% CI, −9.5 to −2.4 cm CSF; $P = .001$) between the groups at 12 months.

Secondary Outcomes

The secondary outcome of LP opening pressure at 24 months demonstrated increasing effect size between 12 and 24 months, with a mean (SE) difference between the 2 arms of −8.2 (2.0) cm CSF (95% CI, −12.2 to −4.2 cm CSF; $P < .001$). In the per protocol analysis, ICP was significantly lower in the surgery arm at 12 months (adjusted mean [SE] difference, −7.2 [1.8] cm CSF; 95% CI, −10.6 to −3.7 cm CSF; $P < .001$) and at 24 months (adjusted mean [SE] difference, −8.7 [2.0] cm CSF; 95% CI, −12.7 to −4.8 cm CSF; $P < .001$) (Table 2). Exploratory analysis showed that the mean (SE) ICP had decreased in the surgery arm from 34.8 (5.8) cm CSF at baseline to 26.9 (8.1) cm CSF at 2 weeks after surgery ($P < .001$) (Table 2 and Figure 2). At 12 months, the mean (SE) percentage change in ICP was −32.1% (4.7%) in the surgery arm compared with −2.5% (3.9%) in the weight management arm ($P < .001$). At 24 months, the mean (SE) percentage change in ICP was −35.0% (4.9%) in the surgery arm compared with −6.0% (3.8%) in the weight management arm ($P < .001$) (Figure 2).

At both 12 and 24 months, all measures of improvement in weight, BMI, and reduction of excess body weight were significantly greater in the surgery arm vs the weight management arm ($P < .001$) (Table 2 and Figure 2), with increased effect between 12 and 24 months. Weight was significantly lower in the surgery arm at 12 months (adjusted mean [SE] difference, −21.4 [5.4] kg; 95% CI, −32.1 to −10.7 kg; $P < .001$) and at 24 months (adjusted mean [SE] difference, −26.6 [5.6] kg; 95% CI, −37.5 to −15.7 kg; $P < .001$) compared with the weight management arm. With regard to the percentage of weight loss (Figure 2) and the percentage of excess weight loss, the mean (SE) difference between groups at 12 months was −18.3% (1.9%;

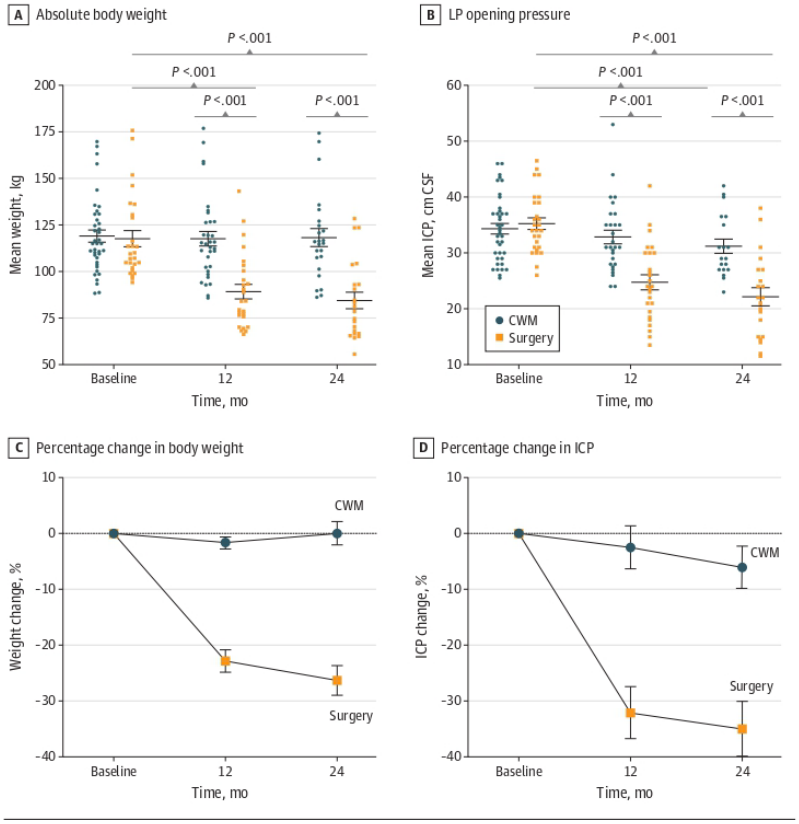
Table 2. Primary Outcome and Anthropometric Features by Treatment Arm

Outcome or feature	Baseline		At surgery		At 2 wk after surgery		At 12 mo		At 24 mo		Difference from baseline to 12 mo			Difference from baseline to 24 mo			Difference between arms at 12 mo			Difference between arms at 24 mo		
											Hierarchical regression			Hierarchical regression			Hierarchical regression			Hierarchical regression		
	Mean (SD)	Participants, No.	Mean (SD)	Participants, No.	Mean (SD)	Participants, No.	Mean (SD)	Participants, No.	Mean (SD)	Participants, No.	Mean (SE)	95% CI	*P* value	Mean (SE)	95% CI	*P* value	Mean (SE)	95% CI	*P* value	Mean (SE)	95% CI	*P* value
ICP (intention to treat), cm CSF																						
CWM intervention	34.6 (5.6)	33	NA	NA	NA	NA	32.0 (5.2)	25	31.0 (5.7)	18	−2.5 (1.4)	−5.2 to 0.3	.08	−3.5 (1.6)	−6.6 to −0.3	.03	−6.0 (1.8)	−9.5 to −2.4	.001	−8.2 (2.0)	−12.2 to −4.2	<.001
Bariatric surgery	34.8 (5.8)	33	NA	NA[a]	26.9 (8.1)	18	26.4 (8.7)	29	22.8 (7.8)	22	−8.7 (1.3)	−11.3 to −6.1	<.001	−11.9 (1.5)	−14.8 to −9.0	<.001						
ICP (per protocol), cm CSF																						
CWM intervention	34.6 (5.9)	33	NA	NA	NA	NA	32.4 (6.5)	26	31.4 (5.9)	17	−1.9 (1.4)	−4.6 to 0.7	.15	−3.0 (1.6)	−6.1 to 0.1	.06	−7.2 (1.8)	−10.6 to −3.7	<.001	−8.7 (2.0)	−12.7 to −4.8	<.001
Bariatric surgery	34.9 (5.4)	30	NA	NA[a]	NA	NA	25.7 (7.5)	28	22.8 (7.4)	23	−9.4 (1.3)	−12.1 to −6.8	<.001	−12.1 (1.4)	−14.9 to −9.3	<.001						
Weight, kg																						
CWM intervention	118.5 (20.7)	33	NA	NA	NA	NA	116.6 (22.3)	29	116.5 (22.9)	22	−2.1 (2.0)	−6.0 to 1.8	.29	−1.4 (2.2)	−5.6 to 2.9	.53	−21.4 (5.4)	−32.1 to −10.7	<.001	−26.6 (5.6)	−37.5 to −15.7	<.001
Bariatric surgery	118.4 (21.8)	33	113.3 (21.7)	27	102.3 (18.8)	18	94.0 (23.7)	30	88.9 (25.9)	24	−23.4 (1.9)	−27.2 to −19.6	<.001	−27.8 (2.1)	−31.9 to −23.8	<.001						
Excess body weight, kg																						
CWM intervention	50.6 (19.4)	33	NA	NA	NA	NA	49.1 (21.3)	29	49.5 (22.1)	22	−1.9 (1.9)	−5.7 to 1.9	.32	−1.3 (2.1)	−5.5 to 2.8	.53	−20.3 (5.1)	−30.3 to −10.2	<.001	−25.8 (5.3)	−36.1 to −15.5	<.001
Bariatric surgery	51.5 (20.0)	33	46.2 (20.0)	27	36.5 (16.4)	18	27.2 (22.3)	30	21.2 (24.9)	24	−23.0 (1.9)	−26.8 to −19.3	<.001	−28.0 (2.1)	−32.0 to −23.9	<.001						
BMI																						
CWM intervention	43.7 (7.1)	33	NA	NA	NA	NA	43.1 (7.8)	29	43.5 (8.0)	22	−0.7 (0.7)	−2.1 to 0.7	.35	−0.4 (0.8)	−1.9 to 1.2	.62	−7.3 (1.9)	−11.0 to −3.7	<.001	−9.4 (1.9)	−13.2 to −5.7	<.001
Bariatric surgery	44.2 (7.1)	33	42.2 (7.1)	27	38.9 (5.7)	18	35.1 (8.0)	30	32.8 (8.9)	24	−8.5 (0.7)	−9.9 to −7.2	<.001	−10.4 (0.8)	−11.8 to −8.9	<.001						

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CSF, cerebrospinal fluid; CWM, community weight management; ICP, intracranial pressure; NA, not applicable.

[a] Intracranial pressure was not assessed until 2 weeks after surgery was performed.

Figure 2. Body Weight, Lumbar Puncture (LP) Opening Pressure, Percentage Change in Body Weight, and Percentage Change in Intracranial Pressure (ICP) by Trial Arm



Whiskers represent SEs.
CSF indicates cerebrospinal fluid; CWM, community weight management.

95% CI, −22.1% to −14.6%; $P < .001$) and −46.4% (4.9%; 95% CI, −56.1% to −36.7%; $P < .001$), respectively. The 24-month results were similar (adjusted mean [SE] difference in weight loss, −23.6% [2.1%; 95% CI, −27.8% to −19.4%]; adjusted mean [SE] difference in excess weight loss, −61.6% [5.5%; 95% CI, −72.3% to −50.8%]; $P < .001$ for both) (Figure 2).

Papilledema was reduced in both arms; from baseline to 12 months, the median Frisén grade decreased from 2 (IQR, 2-3) to 1 (IQR, 1-2) in the surgery arm and from 2 (IQR, 2-3) to 1 (IQR, 1-2) in the weight management arm. Differences in headache disability, as measured by Headache Impact Test scores between the 2 arms, were not significant at 12 months (adjusted mean [SE] difference, −1.4 [2.6]; 95% CI, −6.6 to 3.8; $P = .60$) or 24 months (adjusted mean [SE] difference, −1.4 [2.8]; 95% CI, −7.0 to 4.1; $P = .61$) (eTable 3 in Supplement 2). Exploratory analysis indicated a greater improvement in mean monthly headache days, headache severity, and Headache Impact Test scores in the surgery arm between baseline and 12 months (eTable 3 in Supplement 2). Differences in visual function, as measured by perimetric mean deviation between the 2 arms, were not significant at 12 months (adjusted mean [SE] difference, −0.5 [0.8]; 95% CI, −2.0 to 1.0; $P = .53$) or 24 months (adjusted mean [SE] difference, −0.1 [0.8]; 95% CI, −1.5 to 1.8; $P = .86$) (eTable 4 in Supplement 2). There was no evidence of improvement in IIH symptoms in either group (eTable 5 in Supplement 2).

Analysis of quality of life using the 36-item Short Form Health Survey showed a significant change in the physical component score at 12 months (adjusted mean [SE] difference, 7.3 [3.6]; 95% CI, 0.2-14.4; $P = .04$). This change was also significant at 24 months between the 2 arms (adjusted mean [SE] difference, 10.4 [3.8]; 95% CI, 3.0-17.9; $P = .006$) (eTable 6 in Supplement 2). In addition, significant improvement was observed in the 3 domains of energy and fatigue at 12 months (adjusted mean [SE] difference, 14.9 [6.4]; 95% CI, 2.4-27.4; $P = .02$), in physical functioning at both 12 months (adjusted mean [SE] difference, 20.2 [6.8]; 95% CI, 6.9-33.5; $P = .003$) and 24 months (adjusted mean [SE] difference, 27.7 [7.2]; 95% CI, 13.7-41.8; $P < .001$), and in general health at 24 months (adjusted mean [SE] difference, 22.8 [6.0]; 95% CI, 11.1-34.6; $P < .001$) (eTable 7 in Supplement 2). No other domains showed significant differences (eTable 7 in Supplement 2). Scores from the Hospital Anxiety and Depression Scale showed within-arm improvement in the surgery arm, with changes in scores

on the depression subscale at 12 months (adjusted mean [SE] difference, −1.6 [0.8]; 95% CI, −3.1 to 0; $P = .05$) and 24 months (adjusted mean [SE] difference, −2.7 [0.9]; 95% CI, −4.4 to −1.0; $P = .002$) (eTable 6 in Supplement 2). Relevant medication changes over the course of the clinical trial are available in the eResults in Supplement 2.

Adverse Events

In the whole cohort, 15 SAEs were reported by 12 months, and an additional 9 SAEs were reported by 24 months (eTable 8 in Supplement 2); 18 SAEs were unrelated to the group allocation. The 24 SAEs occurred in 17 participants, with 1 individual experiencing 4 SAEs. Of the 24 SAEs, 9 events were caused by exacerbation of IIH leading to hospitalization. No patients underwent emergency surgery for IIH in the first year. During 12 to 24 months, 1 patient in the weight management arm underwent CSF shunting for deterioration of IIH.

By 24 months, 6 related SAEs were reported in the whole cohort. One related SAE in the weight management arm was a post-LP headache. The 5 related SAEs in the surgery arm included 4 events that were treated conservatively, comprising 1 post-LP headache, 1 delayed discharge immediately after surgery, and 1 hospital admission each for vomiting and epigastric pain, both of which resolved spontaneously. One SAE comprised a hospital admission with vomiting, which was identified through diagnostic laparoscopy to be caused by obstruction at the site of the mesenteric closure. The mesenteric stitch was removed, and the participant experienced no further events. There were no deaths in the 24-month period among participants in either group.

Discussion

To our knowledge, the IIH:WT is the first randomized clinical trial to evaluate the efficacy of bariatric surgery compared with a community weight management intervention among patients with active IIH. A significant difference was found in the primary outcome of ICP at 12 months. Reduction in ICP among patients with IIH has been associated with disease remission, which enables papilledema resolution and improvement in headache symptoms.[6] The results of this clinical trial therefore support the use of bariatric surgery as an effective treatment approach among patients with active IIH who have a BMI of 35 or higher, with an enduring effect at 24 months.

Idiopathic intracranial hypertension has been reported to adversely affect patients' quality of life.[2] The IIH:WT documented significant improvements in physical component score, energy and fatigue physical functioning, and general health (eTable 7 and eTable 8 in Supplement 2) after bariatric surgery. At 24 months, there were significant differences in outcomes, supporting the use of bariatric surgery for the improvement of physical functioning and general health (eTable 8 in Supplement 2). These improvements could reflect the receipt of bariatric surgery because this surgery is associated with benefits for quality of life as well as with IIH remission.[21] No improvements in mental component scores were observed in other domains, which is consistent with the findings of a meta-analysis comprising clinical trials that examined bariatric surgery.[22]

Bariatric surgery delivers a wider range of health benefits compared with conservative medical methods for weight loss.[23] A meta-analysis reported that Roux-en-Y gastric bypass surgery was associated with better outcomes compared with other types of bariatric procedures and weight management programs.[24] Roux-en-Y gastric bypass surgery has also been associated with a reduced risk of cardiovascular disease compared with routine care.[12]

These cardiovascular improvements and their positive implications for other comorbidities, such as polycystic ovarian syndrome, may be of additional benefit for those with IIH because IIH is associated with a 2-fold increased risk of worse cardiovascular outcomes[4] and polycystic ovarian syndrome.[1] Future clinical trials should investigate which type of bariatric surgical procedure is superior for patients with IIH.

The complication rates of bariatric surgery have improved over time, with the mortality rate currently reported to be 0% to 0.64%.[25] In the IIH:WT, both trial withdrawal and SAE rates were low, with only 1 participant requiring further surgical intervention.

Limitations

This study has several limitations. The type of bariatric procedure was not predetermined for the surgical arm because the development of the study design was based on pragmatic considerations to reflect routine clinical practice. As a consequence, the number of participants in the trial was too low to confidently recommend 1 surgical procedure over another. This clinical trial was also unable to evaluate patient-centered outcomes because of the relatively low number of participants required to power the study to achieve its primary outcome. Powering the study to achieve meaningful secondary outcome analyses would have required a 5-fold increase in the number of participants. Therefore, we were not able to develop meaningful inferences about the effects of bariatric surgery on the secondary outcomes.

For practical reasons, the physicians performing the LPs were not masked to the results. Although they were masked to the treatment arms to which the participants had been assigned, the difference in weight loss between the 2 arms would have made complete masking a challenge. Applying the results of this clinical trial to a broader population of participants with IIH is limited by the study's inclusion criteria; thus, the findings do not directly inform treatment among men or women with a BMI lower than 35. These individuals may benefit from bariatric surgery because it has been reported to have favorable metabolic and glycemic implications for those with a BMI between 30 and 35.[23]

Conclusions

In this randomized clinical trial, bariatric surgery among patients with active IIH had favorable sustained outcomes with regard to reductions in ICP, disease remission, and superior quality of life outcomes at 2 years compared with a commu-

nity weight management intervention. These results can be used to develop recommendations for health care strategies and to inform health policy decisions regarding bariatric surgery for individuals with active IIH.

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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Clinical Trial Investigators and Sites, Bariatric Surgery Pathway Team, Patient Identification Centers, and Study Oversight Committees

Trial Investigators
Chief Investigator: Professor. Alex Sinclair Trial Manager: Mr Ryan Ottridge
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Leicester General Hospital, University Hospitals of Leicester NHS trust: Dr Mark Lawden.
Royal Stoke University Hospital, University Hospitals of North Midlands NHS Foundation Trust: Dr Brendan Davies.
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Study oversight committees
We thank all the members of the study oversight committees for their valued contributions. The IIH:WT Trial Steering Committee; the Data Monitoring and Ethics Committee and the Trial Management Group.

eMethods 2. Community Weight Management Intervention, Bariatric Surgery Pathway, and Hierarchical Regression Analysis

Community weight management intervention

WeightWatchers™ program was chosen as the community weight management intervention (CWI) because it had superior weight loss[1], was the best attended and most cost-effective[2]. Participants in the CWI arm were given exemption vouchers for 52 consecutive and specified weeks of their local WeightWatchers™ group with access to WeightWatchers™ online and mobile tools for 12 months. Vouchers provided 12 sessions at baseline, 3, 6 and 9 months.

Bariatric surgery pathway

The bariatric surgery pathway participants were screened to ensure their suitability, initially for medical and psychological assessment in the weight management clinic. This assessment continued for as long as thought appropriate, as per routine care. Once suitable, the case was discussed in the joint multi-disciplinary meeting, prior a group session for education regarding surgery. The participant then attended a consultant bariatric surgeon and was given a date for surgery. Twelve weeks was permitted for further consideration of the procedure if required. The standard patient pathway was envisioned to take approximately 4 months. The choice of surgical intervention was decided between the surgeon and participant, based on the participant's health and preference. These included laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy.

Hierarchical regression analysis

Initially, hierarchical regression models were generated, with data for both eyes for all patients analyzed in one model, using group structure to distinguish between the eyes. Models contained population-level terms (i.e. terms that apply to each experimental unit) to reflect: 1) the mean baseline value (i.e. the intercept); 2) the mean change from baseline associated with each assessment time (i.e. time as a factor variable); 3) the extra mean change from baseline associated with each assessment time in the experimental arm (i.e. the interaction of treatment allocation and time as a factor variable). Additionally, hierarchical regression models contained random effects (i.e. terms that are specific to each experimental unit) to reflect the random deviations from the population-level mean value at baseline (i.e. random intercepts).

eResults. Relevant Medication Changes Over the Course of the Clinical Trial

Headache preventative medication was taken by 27% (18/66) of all patients at enrolment. This reduced markedly amongst the bariatric surgery arm from 36% (12/33) at baseline to 7% (2/30) at 12 months, compared with little difference in the CWI arm from baseline 18% (6/33) to 21% (6/29) at 12 months. Acetazolamide was taken by 29% (19/66) of all patients at enrolment. The number of patients using acetazolamide reduced amongst those in the bariatric surgery arm from 24% (8/33) to 3% (1/30) with a mean daily dose change from 781mg (471.3) to 500mg (standard deviation [SD] 0) compared with the CWI arm whose numbers using acetazolamide reduced from 33% (11/33) to 28% (8/33) with a mean daily dose change from 909mg (SD 550.8) to 844mg (SD 498.9). Topiramate was used by 12% (4/33) in the bariatric surgery arm at baseline. All had discontinued by 12 months, whilst in the CWI arm 6% (2/33) topiramate use increased to 10% (3/29) by 12 months. Those taking other diuretics were 3% (1/33) in bariatric surgery arm and 6% (2/33) in the CWI arm at baseline. By 12 months, 3% (1/30) were using a diuretic in the bariatric surgery arm and 10% (3/29) in the CWI arm. There were no significant differences in the use of antihypertensive medications or hormonal contraception.

eTable 1. Inclusion and Exclusion Criteria of the IIH:WT

	Criterion
Inclusion	Female patients with IIH aged between 18 and 55 years, diagnosed according to the Friedman Jacobson criteria,[1] who have active disease [papilloedema (Frisén[2] grade ≥1 in at least one eye), significantly raised LP OP ≥25 cmCSF] of over 2 months' duration and no evidence of venous sinus thrombosis (MRI or CT and venography as noted at diagnosis)
	Body mass index of ≥35 kg/m^2.
	Have previously tried other appropriate non-surgical treatments to lose weight but have not been able to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months.
	Able to give informed consent.
Exclusion	Age <18 or >55 years.
	Pregnancy, or planning pregnancy.
	Significant comorbidity, Cushing's syndrome, Addison's disease or the use of oral or injected glucocorticoid therapy.
	Previously undergone optic nerve sheath fenestration
	Definite indication for or contraindication against surgery or dieting
	Have a specific medical or psychiatric contraindication for surgery, including drug misuse, eating disorder or major depression (suicidal ideation, drug overdose or psychological admission in the last 12 months).
	Previous bariatric surgery
	Inability to give informed consent, for example, due to cognitive impairment.

References to eTable 1:

1. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology*. 2013; 81(13):1159-1165.
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eTable 2. IIH:WT Schedule of Events

Outcome	Measure	Baseline	3 months	6 months	Postoperative	12 months (primary endpoint)	24 months	60 months
Intracranial pressure	Lumbar puncture opening pressure	x			x	x	x	x
Clinical measures	Body mass index, blood pressure, waist/hip, fat mass, medication use	x	x	x	x	x	x	x
Idiopathic Intracranial Hypertension symptoms	Pulsatile tinnitus, visual loss, diplopia, visual obscurations	x				x	x	x
Visual function	Visual acuity, contrast sensitivity, colour assessment	x				x	x	x
	Humphrey visual field (24–2)	x				x	x	x
Papilledema grade	Optical coherence tomography	x				x	x	x
	Retinal photographs	x				x	x	x
Headache	HIT-6, headache diary	x				x	x	x
Quality of life	EQ-5D-5L, ICECAP-A, SF-36 v1, HADS	x				x	x	x
Health economics	Resource use questionnaire	x				x	x	x

HIT-6 = Headache impact test-6. EQ-5D-5L= ICECAP-A= SF-36v1=, HADS=Hospital anxiety and depression score.

eTable 3. Secondary Outcome: Headache

Differences in headache and visual function outcomes were not significant at 12- or 24-months (eTables 3 and 4). Exploratory analysis noted a greater improvement in monthly headache days, headache severity and HIT-6 scores in the bariatric surgery arm between baseline and 12-months (eTable 3).

	Baseline	12 months	24 months	Difference baseline to 12 months	Difference baseline to 12 months	Difference baseline to 24 months	Difference between arms at 12 months	Difference between arms at 24 months
					Hierarchical regression			
	Mean (SD), n			Mean (SD); 95%CI, p	Mean (SE); 95%CI, p			
Headache disability (HIT-6)								
Community weight management intervention	64.3 (8.6), 32	59.7 (12.4), 26	60.2 (10.9), 23	-6.2 (9.8), 28	-5.3 (1.9); (-9.1, -1.5), p=0.006	-5.7 (2.0); (-9.7, -1.8), p=0.004	-1.4 (2.6); (-6.6, 3.8), p=0.603	-1.4 (2.8); (-7.0, 4.1), p=0.610
Bariatric surgery	65.1 (6.0), 33	57.5 (9.1), 29	56.5 (13.0), 23	-7.4 (8.6), 29	-7.5 (1.9); (-11.1, -3.9), p<0.001	-8.0 (2.0); (-11.9, -4.0), p<0.001		
Monthly headache days								
Community weight management intervention	22.5 (7.8), 31	16.7 (11.8), 24	15.8 (11.1), 21	-6.3 (9.9), 23	-5.9 (2.2); (-10.2, -1.6), p=0.007	-7.4 (2.3); (-11.9, -2.9), p=0.001	-3.2 (2.8); (-8.6, 2.2), p=0.247	-2.9 (3.0); (-8.7, 2.9), p=0.328
Bariatric surgery	22.0 (8.3), 32	13.2 (11.4), 29	11.8 (11.8), 24	-8.1 (10.5), 28	-8.5 (2.0); (-12.5, -4.5), p<0.001	-9.7 (2.2); (-13.9, -5.5), p<0.001		
Monthly analgesic frequency								
Community weight management intervention	14.1 (9.4), 31	10.2 (10.5), 24	9.0 (9.5), 21	..	-3.7 (2.1); (-7.9, 0.5), p=0.085	-6.0 (2.2); (-10.4, -1.6), p=0.008	-3.0 (2.6); (-8.1, 2.2), p=0.257	1.2 (2.8); (-4.3, 6.7), p=0.665
Bariatric surgery	10.6 (8.5), 32	7.3 (9.1), 29	9.3 (11.0), 24	..	-3.1 (2.0); (-7.0, 0.9), p=0.125	-1.2 (2.1); (-5.3, 2.9), p=0.570		
Headache severity (VRS 0-10)								
Community weight management intervention	5.0 (2.1), 31	4.0 (3.3), 24	3.8 (3.0), 21	-1.1 (2.5), 22	-1.0 (0.6); (-2.2, 0.2), p=0.110	-1.5 (0.6); (-2.7, -0.2), p=0.023	-0.9 (0.7); (-2.3, 0.6), p=0.231	0.2 (0.8); (-1.3, 1.7), p=0.796
Bariatric surgery	5.0 (1.9), 32	3.2 (2.6), 29	3.8 (3.1), 24	-1.6 (2.7), 28	-1.8 (0.6); (-2.9, -0.7), p=0.002	-1.2 (0.6); (-2.4, 0.0), p=0.045		

CI=confidence interval. SD=standard deviation. SE=standard error.

eTable 4. Secondary Outcome: Visual Data (Worst Eye)

	Baseline	**12 months**	**24 months**	**Difference baseline to 12 months**	**Difference baseline to 12 months**	**Difference baseline to 24 months**	**Difference between arms at 12 months**	**Difference between arms at 24 months**
	Mean (SD), n			Mean (SD); 95%CI, p	Hierarchical regression Mean (SE); 95%CI, p			
logMar visual acuity								
Community weight management intervention	0.0 (0.2), 33	0.0 (0.2), 28	0.0 (0.2), 21	-0.02 (0.20)	0.0 (0.1); (-0.1, 0.1), p=0.985	0.0 (0.1); (-0.1, 0.1), p=0.661	0.0 (0.1); (-0.1, 0.1), p=0.598	0.0 (0.1); (-0.1, 0.1), p=0.988
Bariatric surgery	0.0 (0.2), 33	0.0 (0.2), 30	-0.1 (0.1), 24	-0.08 (0.24)	-0.1 (0.1); (-0.2, 0.0), p=0.058	-0.1 (0.1); (-0.1, 0.0), p=0.120		
Log contrast sensitivity								
Community weight management intervention	1.7 (0.1), 33	1.7 (0.1), 28	1.7 (0.1), 21	..	0.0 (0.1); (0.0, 0.1), p=0.630	0.0 (0.1); (0.0, 0.1), p=0.584	0.0 (0.1); (-0.1, 0.0), p=0.411	0.0 (0.1); (-0.1, 0.1), p=0.951
Bariatric surgery	1.7 (0.1), 33	1.7 (0.1), 29	1.7 (0.1), 24	..	0.0 (0.1); (0.0, 0.1), p=0.463	0.1 (0.1); (0.0, 0.1), p=0.066		
Perimetric mean deviation, dB (HVF 24-2 SITA standard)								
Community weight management intervention	-3.5 (3.8), 33	-2.0 (2.3), 29	-2.1 (2.8), 22	1.2 (2.6)	1.3 (0.5); (0.3, 2.3), p=0.010	1.5 (0.6); (0.4, 2.6), p=0.010	-0.5 (0.8); (-2.0, 1.0), p=0.526	0.1 (0.8); (-1.5, 1.8), p=0.863
Bariatric surgery	-3.6 (3.5), 32	-2.8 (2.6), 29	-2.2 (2.2), 24	1.1 (2.7)	1.0 (0.5); (-0.1, 2.0), p=0.064	1.8 (0.6); (0.7, 2.8), p=0.002		
Optical Coherence Tomography retinal nerve fibre layer in more affected (worst) eye (µm)								
Community weight management intervention	161.7 (95.7), 32	111.8 (33.1), 28	107.4 (31.9), 22	-56 (88.3), 27	-50.5 (15.9); (-81.7, -19.3), p=0.001	-53.0 (17.1); (-86.6, -19.4), p=0.002	-8.1 (17.3); (-41.9, 25.8), p=0.641	-7.7 (19.6); (-46.1, 30.7), p=0.695
Bariatric surgery	148.8 (99.1), 32	103.0 (27.4), 29	103.0 (27.3), 22	-43 (107.3), 29	-45.3 (15.7); (-76.1, -14.5), p=0.004	-47.4 (17.1); (-80.9, -13.9), p=0.006		

All visual function measures are of worst eye. Negative values in the mean difference and adjusted mean difference favour surgical arm. SD=standard deviation. CI=confidence interval. HVF- Humphrey visual field.

eTable 5. IIH Symptoms, Baseline to 12 Months

There was no evidence of improvement in the IIH symptoms of pulsatile tinnitus, visual symptoms, diplopia and visual obscurations in either group (eTable 5).

	Baseline		**12 months**		**Relative Risk***	**p**
	Community weight management	**Bariatric surgery**	**Community weight management**	**Bariatric surgery**	**(95% CI)**	
Pulsatile Tinnitus						
Not experienced	8 (24)	9 (27)	11(38)	16(53)	0.76 (0.50 to 1.17)	0.2
Experienced	25 (76)	24 (73)	18(62)	14(47)		
Visual Loss						
Not experienced	10 (30)	8 (24)	15(52)	20(67)	0.69 (0.37 to 1.30)	0.2
Experienced	23 (70)	25 (76)	14(48)	10(33)		
Diplopia						
Not experienced	29 (88)	19 (58)	25(86)	26(87)	0.33 (0.07 to 1.67)	0.2
Experienced	4 (12)	14 (42)	4(14)	4(13)		
Visual Obscurations						
Not experienced	16 (48)	16 (48)	25(86)	23(77)	1.53 (0.54 to 4.35)	0.4
Experienced	17 (52)	17 (52)	4(14)	7(23)		
Headache						
Not experienced	1 (3)	2 (6)	6(21)	8(27)	0.98 (0.67 to 1.44)	0.9
Experienced	32 (97)	31 (94)	23(79)	22(73)		

Data are n(%) unless otherwise stated.*Adjusted for baseline IIH symptoms and acetazolamide use at entry (stratification variable). Relative risk less than 1 favours bariatric surgery.

CI = confidence intervals.

eTable 6. Quality of Life and Hospital Anxiety and Depression Scores

	Base line	**12 month**	**24 month**	**Difference baseline to 12 months**	**Difference baseline to 24 months**	**Difference between arms at 12 months**	**Difference between arms at 24 months**
	Mean (SD), n			Hierarchical regression mean (SE); 95%CI, p		Hierarchical regression mean (SE); 95%CI, p	
Quality of Life							
Quality of life (SF-36) PCS summary							
Community weight management intervention	29.1 (12.2), 30	33.4 (14.8), 25	32.0 (13.8), 22	4.5 (2.6); (-0.5, 9.6), p=0.079	4.5 (2.8); (-0.9, 9.9), p=0.099	7.3 (3.6); (0.2, 14.4), p=0.043	10.4 (3.8); (3.0, 17.9), p=0.006
Bariatric Surgery	28.3 (13.4), 30	41.6 (14.0), 28	45.2 (12.0), 23	13.1 (2.5); (8.1, 18.0), p<0.001	16.2 (2.7); (10.9, 21.5), p<0.001		
Quality of life (SF-36) MCS summary							
Community weight management intervention	35.8 (10.2), 30	37.9 (12.0), 25	39.6 (12.6), 22	2.1 (2.4); (-2.6, 6.9), p=0.384	4.3 (2.6); (-0.8, 9.3), p=0.097	1.6 (3.2); (-4.6, 7.8), p=0.617	-0.5 (3.4); (-7.1, 6.1), p=0.876
Bariatric Surgery	39.7 (11.5), 30	39.8 (12.5), 28	39.8 (12.4), 23	-0.1 (2.4); (-4.7, 4.6), p=0.981	0.0 (2.6); (-5.0, 5.0), p=0.998		
Hospital anxiety and depression scores							
HADS -A							
Community weight management intervention	10.5 (4.6), 32	10.5 (5.2), 26	9.7 (5.6), 21	-0.1 (0.9); (-1.8, 1.6), p=0.925	-1.2 (0.9); (-3.1, 0.6), p=0.179	-1.1 (1.3); (-3.7, 1.5), p=0.405	-0.2 (1.4); (-3.0, 2.6), p=0.887
Bariatric Surgery	10.5 (5.1), 30	9.5 (4.8), 28	9.0 (5.8), 24	-1.1 (0.9); (-2.8, 0.6), p=0.202	-1.3 (0.9); (-3.1, 0.4), p=0.142		
HADS-D							
Community weight management intervention	7.9 (4.8), 32	7.3 (4.2), 27	7.0 (5.0), 22	-0.3 (0.8); (-1.9, 1.3), p=0.727	-1.5 (0.9); (-3.3, 0.2), p=0.082	-1.6 (1.2); (-4.0, 0.8), p=0.200	-1.5 (1.3); (-4.0, 1.1), p=0.268
Bariatric Surgery	7.6 (4.1), 31	6.2 (5.1), 30	4.8 (4.9), 24	-1.6 (0.8); (-3.1, 0.0), p=0.053	-2.7 (0.9); (-4.4, -1.0), p=0.002		

Data are mean (SD) or mean (SE).

SD=standard deviation. SE=standard error. CI=confidence interval. HIT-6 = Headache impact test-6. HADS=Hospital anxiety and depression score. SD = standard deviation. SE = standard error. SF-36 = 36-item short form survey.

eTable 7. Quality of Life Subscales as Measured by the SF-36

	Baseline	12 months	24 months	Difference baseline to 12 months	Difference baseline to 24 months	Difference between arms at 12 months	Difference between arms at 24 months
				Hierarchical regression mean (SE); 95%CI, p			
Physical functioning							
Community weight management	56.8 (26.1), 31	62.6 (30.6), 27	59.6 (30.1), 23	4.1 (4.3); (-4.2, 12.5), p=0.331	6.6 (4.5); (-2.3, 15.5), p=0.144	20.2 (6.8); (6.9, 33.5), p=0.003	27.7 (7.2); (13.7, 41.8), p<0.001
Bariatric Surgery	56.6 (27.5), 32	81.9 (22.9), 29	92.6 (13.3), 23	24.7 (4.1); (16.6, 32.8), p<0.001	34.6 (4.5); (25.8, 43.5), p<0.001		
Role limitation due to physical health							
Community weight management	28.1 (40.5), 32	43.3 (47.2), 26	46.7 (43.5), 23	17.4 (8.8); (0.2, 34.6), p=0.047	24.4 (9.2); (6.4, 42.3), p=0.008		
Bariatric Surgery	36.4 (44.2), 33	56.0 (43.6), 29	57.3 (46.9), 24	9.7 (8.4); (3.2, 36.2), p=0.019	21.1 (9.0); (3.5, 38.8), p=0.019	10.5 (11.8); (-12.5, 33.6), p=0.371	5.0 (12.5); (-19.4, 29.5), p=0.687
Role limitation due to emotional problems							
Community weight management	37.6 (43.7), 31	51.3 (46.4), 26	53.6 (46.9), 23	13.2 (10.0); (-6.4, 32.8), p=0.186	19.2 (10.4); (-1.3, 39.6), p=0.066		
Bariatric Surgery	45.8 (45.4), 32	57.5 (47.9), 29	65.2 (44.4), 23	11.6 (9.6); (-7.2, 30.4), p=0.226	19.5 (10.4); (-0.9, 39.9), p=0.060	5.9 (12.2); (-18.0, 29.8), p=0.627	7.9 (13.1); (-17.9, 33.6), p=0.550
Energy/Fatigue							
Community weight management	28.0 (18.2), 32	33.7 (27.4), 27	36.1 (23.9), 23	5.7 (4.8); (-3.8, 15.1), p=0.242	10.8 (5.1); (0.7, 20.8), p=0.035		
Bariatric Surgery	26.1 (20.8), 33	49.0 (26.7), 29	46.5 (28.8), 24	22.4 (4.7); (13.2, 31.7), p<0.001	20.1 (5.0); (10.3, 30.0), p<0.001	14.9 (6.4); (2.4, 27.4), p=0.020	7.5 (6.8); (-5.9, 20.9), p=0.275
Emotional well-being							
Community weight management	50.5 (23.6), 32	56.0 (27.3), 27	52.7 (27.8), 23	5.3 (4.4); (-3.4, 14.0), p=0.232	5.2 (4.7); (-4.0, 14.5), p=0.268		
Bariatric Surgery	55.0 (26.3), 33	59.2 (26.0), 29	59.8 (29.4), 24	3.1 (4.3); (-5.4, 11.6), p=0.476	5.0 (4.6); (-4.0, 14.1), p=0.277	2.3 (6.9); (-11.2, 15.8), p=0.738	4.3 (7.2); (-9.9, 18.5), p=0.550

Social functioning							
Community weight management	46.9 (8.4), 32	48.6 (6.3), 27	50.5 (10.3) , 23	1.8 (2.4); (-2.9, 6.5), p=0.450	3.6 (2.5); (-1.3, 8.5), p=0.145		
Bariatric Surgery	55.3 (11.3) , 33	50.4 (10.3) , 29	49.5 (8.6), 24	-4.9 (2.3); (-9.4, -0.3), p=0.036	-5.9 (2.4); (-10.7, -1.1), p=0.016	1.8 (2.5); (-3.2, 6.7), p=0.482	-1.1 (2.7); (-6.5, 4.2), p=0.680
Pain							
Community weight management	45.6 (26.2) , 32	51.6 (30.4) , 26	43.5 (30.0) , 22	6.9 (5.9); (-4.6, 18.4), p=0.237	2.5 (6.2); (-9.7, 14.7), p=0.688		
Bariatric Surgery	42.9 (25.6) , 32	62.4 (27.4) , 28	61.5 (31.0) , 24	18.4 (5.7); (7.2, 29.6), p=0.001	17.4 (6.1); (5.5, 29.3), p=0.004	8.4 (7.6); (-6.5, 23.3), p=0.267	11.9 (8.1); (-4.0, 27.7), p=0.143
General health							
Community weight management	34.1 (18.7) , 32	39.4 (19.7) , 27	32.8 (21.7) , 23	4.7 (4.1); (-3.3, 12.7), p=0.247	0.3 (4.3); (-8.2, 8.7), p=0.949		
Bariatric Surgery	30.8 (17.6) , 33	49.0 (24.0) , 29	58.3 (27.8) , 24	17.9 (4.0); (10.2, 25.7), p<0.001	26.4 (4.2); (18.1, 34.7), p<0.001	9.9 (5.6); (-1.2, 20.9), p=0.079	22.8 (6.0); (11.1, 34.6), p<0.001

Data are mean (SD) or mean (SE).

CI = confidence intervals. SD = standard deviation. SE = standard error. SF-36 = 36-item short form survey.

eTable 8. Serious Adverse Events at 12 and 24 Months

Time following randomisation	Community weight management intervention		Bariatric surgery		Total
	Related	Unrelated	Related	Unrelated	
0-12months	0	3 (3)	4	8 (6)	15
12-24months	1*	7 (4)	1	0 (0)	9
Total	1	10 (7)	5	8 (6)	24

Data are n. Those in brackets are the number of events that are a hospitalised episode of exacerbation of idiopathic intracranial hypertension.

* This participant had a headache following lumbar puncture as part of the trial, which was therefore assigned as a related serious adverse event headache. Adverse events are presented by Medical Dictionary for Regulatory Activities preferred term.

Publication 6: Association of Amount of Weight Lost After Bariatric Surgery With Intracranial Pressure in Women With Idiopathic Intracranial Hypertension

Manuscript title:
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I helped interpret the per protocol analysis. I wrote the initial draft of the publication. I revised the publication following critical internal and external review.

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RESEARCH ARTICLE OPEN ACCESS

Association of Amount of Weight Lost After Bariatric Surgery With Intracranial Pressure in Women With Idiopathic Intracranial Hypertension

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Abstract

Background and Objectives

The idiopathic intracranial hypertension randomized controlled weight trial (IIH:WT) established that weight loss through bariatric surgery significantly reduced intracranial pressure when compared with a community weight management intervention. This substudy aimed to evaluate the amount of weight loss required to reduce intracranial pressure and to explore the effect of different bariatric surgical approaches.

Methods

IIH:WT was a multicenter randomized controlled trial. Adult women with active idiopathic intracranial hypertension and a body mass index ≥35 kg/m^2 were randomized to bariatric surgery or a community weight management intervention (1:1). This per-protocol analysis evaluated the relationship between intracranial pressure, weight loss, and the weight loss methods. A linear hierarchical regression model was used to fit the trial outcomes, adjusted for time, treatment arm, and weight.

Results

Sixty-six women were included, of whom 23 had received bariatric surgery by 12 months; the mean age was 31 (SD 8.7) years in the bariatric surgery group and 33.2 (SD 7.4) years in the dietary group. Baseline weight and intracranial pressure were similar in both groups with a mean weight of 119.5 (SD 24.1) and 117.9 (SD 19.5) kg and mean lumbar puncture opening pressure of 34.4 (SD 6.3) and 34.9 (SD 5.3) cmCSF in the bariatric surgery and dietary groups, respectively. Weight loss was significantly associated with reduction in intracranial pressure ($R^2 = 0.4734$, $p \leq 0.0001$). Twenty-four percentage of weight loss (weight loss of 13.3 kg [SD 1.76]) was associated with disease remission (intracranial pressure [ICP] ≤ 25 cmCSF). Roux-en-Y gastric bypass achieved greater, more rapid, and sustained ICP reduction compared with other methods.

Discussion

The greater the weight loss, the greater the reduction in ICP was documented. Twenty four percentage of weight loss was associated with disease remission. Such magnitude of weight loss was unlikely to be achieved without bariatric surgery, and hence, consideration of referral to a bariatric surgery program early for those with active idiopathic intracranial hypertension may be appropriate.

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Glossary

BMI = body mass index; **CWI** = community weight management intervention; **HIT-6** = headache impact test-6; **ICP** = intracranial pressure; **IIH** = idiopathic intracranial hypertension; **RYGB** = Roux-en-Y gastric bypass; **WT** = weight trial.

Trial Registration

ClinicalTrials.gov Identifier: NCT02124486; ISRCTN registry number ISRCTN40152829; doi.org/10.1186/ISRCTN40152829.

Classification of Evidence

This study provides Class II evidence that weight loss after bariatric surgery results in reduction in intracranial pressure in adult women with idiopathic intracranial hypertension. This study is Class II because of the use of a per-protocol analysis.

Idiopathic intracranial hypertension (IIH) is characterized by raised intracranial pressure (ICP) that causes chronic headaches and papilledema with the risk of permanent visual loss.[1-3] Both the incidence and prevalence of IIH in preceding decades has increased,[4-6] linked with the worldwide obesity epidemic.[7]

Modest weight gain (approximately 5% were people with obesity) is associated with an increased risk of developing IIH, and in those people who do not have obesity, recent weight gain is a risk.[8,9] Above a body mass index (BMI) threshold of 30 kg/m^2, the incidence of the disease has been shown to exponentially increase as the BMI increases.[5] Increased body weight, particularly visceral adiposity, drives the disease.[10,11] Recent research has shown that IIH has metabolic underpinnings, and patents with IIH have been shown to have unique androgen signatures when compared with people of the same sex, age, and body weight.[12-14] Those with IIH were more likely to have insulin resistance and hyperleptinemia compared with matched controls.[15] IIH adipose has a different transcriptional profile compared with that of matched controls, which predisposes them to lipolysis and weight gain. In addition, adipose tissue metabolism in patients with IIH has differential substrate utilization in keeping with tissue primed for lipolysis and weight gain.[15]

Weight loss is known to be an effective treatment for IIH, with a reduction in body weight of between 3% and 15% inducing disease remission, defined by ICP normalization and papilledema resolution.[16,17] However, maintaining weight loss is challenging, and in general, lost weight will be regained over a 2- to 5-year period.[18] For those with IIH, this could result in multiple recurrences, with the risk of sight loss and chronic headaches.[8,15,19] Sustained weight loss in IIH is therefore necessary to modify the disease and prevent relapses.[1,19] However, the amount of weight loss required to reduce ICP has not been established and has been highlighted as a gap in knowledge with direct clinical relevance.[20]

The IIH:weight trial (IIH:WT) was the first randomized clinical trial to evaluate the efficacy of bariatric surgery compared with a community weight management intervention among patients with active IIH.[21] Reductions in ICP, disease remission, and superior quality of life outcomes at 2 years were reported when compared with a community weight management intervention (CWI).[22] The aim of this per-protocol analysis of IIH:WT was to evaluate the amount of weight loss required to reduce ICP and investigate whether there were differences between weight loss surgery methods.

Methods

IIH:WT was a 5-year randomized, controlled, parallel-group, multicenter trial.[20] IIH:WT recruited participants at 5 UK National Health Service (NHS) hospitals between July 25 2014 and May 25 2017. The trial protocol detailed inclusion and exclusion criteria, in which those who were pregnant or planning pregnancy during the course of the trial were excluded.[21] The sample size calculation and considerations, randomization methods, and outcome measures have been published.[21,22] Written informed consent was obtained from all participants (or guardians of participants) in the study. Women aged between 18 and 55 years, with a BMI ≥35 kg/m^2, who had failed to lose or maintain weight loss, and who had a clinical diagnosis of active IIH[23] were randomized into a 1:1 ratio to either WeightWatchers, the chosen CWI, or a bariatric surgery pathway, stratified by the use or nonuse of acetazolamide. However, not everyone received their treatment allocation. This per-protocol analysis was conducted for the primary outcome as part of a planned secondary analysis. Six participants in the surgery arm did not receive bariatric surgery based on personal choice, and no participants were medically declined for surgery. The per-protocol analysis population was defined as the bariatric surgery arm where participants had undergone surgery within 12 months of randomization and the diet weight management arm where participants did not undergo bariatric surgery by 12 months.

The outcome measures included ICP as measured by lumbar puncture opening pressure; anthropometrics; and perimetric mean deviation using Humphrey 24-2 Swedish Interactive Thresholding Algorithm central threshold automated

Table 1 Baseline Characteristics of the IIH:WT Participants As Per Protocol

	Baseline characteristics mean (SD), number					
		Bariatric surgery				
	Total cohort (n = 66)	All (n = 23)	RYGB (n = 13)	LGB (n = 6)	LSG (n = 4)	Diet weight management (n = 43)
Age (y)	32.5 (7.8), 66	31.3 (8.7), 23	31.5 (8.3), 13	31.3 (11.4), 6	31.1 (7.5), 4	33.2 (7.4), 43
ICP (cmCSF)	34.7 (5.7), 66	34.4 (6.3), 23	34.5 (6.3), 13	33.0 (7.7), 6	36.2 (5.2), 4	34.9 (5.3), 43
Weight (kg)	118.5 (21.1), 66	119.5 (24.1), 23	119.7 (27.5), 13	122.0 (20.5), 6	115.2 (22.2), 4	117.9 (19.5), 43
Excess body weight (kg)	51.1 (19.6), 66	53.0 (21.9), 23	53.0 (26.2), 13	55.6 (17.1), 6	48.9 (16.2), 4	50.0 (18.3), 43
Body mass index (kg/m^2)	43.9 (7.1), 66	44.8 (7.7), 23	44.9 (9.4), 13	45.8 (5.5), 6	43.1 (4.4), 4	43.4 (6.7), 43
OCT global peripapillary retinal nerve fiber layer thickness worse eye (μm)	155.2 (96.8), 64	153.3 (113.6), 22	173.8 (145.4), 12	126.8 (49.3), 6	131.5 (70.4), 4	156.3 (88.3), 42
OCT optic nerve head volume central thickness worse eye (μm)	643.6 (187.8), 46	632.9 (262.4), 16	575.9 (231.7), 8	623.5 (192.3), 4	756.5 (391.2), 4	649.2 (137.9), 30
Perimetric mean deviation worst eye (dB)	−3.6 (3.7), 65	−3.5 (4.0), 23	−3.4 (3.9), 13	−2.1 (1.9), 6	−5.8 (6.4), 4	−3.6 (3.5), 42
Monthly headache days	22.2 (8.0), 63	21.1 (8.9), 22	22.2 (7.9), 13	17.6 (11.9), 5	22.0 (9.5), 4	22.8 (7.5), 41
Headache severity (VRS 0–10)	5.0 (2.0), 63	4.8 (2.0), 22	5.3 (1.6), 13	3.7 (2.3), 5	4.3 (2.6), 4	5.2 (2.0), 41
HIT-6 score	64.7 (7.3), 65	64.2 (5.5), 23	63.8 (5.2), 13	62.5 (6.6), 6	68.2 (4.0), 4	65.0 (8.2), 42

Abbreviations: HIT-6 = headache impact test-6; ICP = intracranial pressure; LGB = laparoscopic gastric band; LSG = laparoscopic sleeve gastrectomy; OCT = optical coherence tomography; RYGB = Roux-en-Y gastric bypass; VRS = verbal rating scale.

perimetry. Optic nerve head swelling was assessed using spectral domain optical coherence tomography (Spectralis, Heidelberg Engineering) using both the global peripapillary retinal nerve fiber layer thickness and the disc volume central thickness measurements. Headache was evaluated using the headache impact test-6 disability questionnaire (HIT-6), severity scores (numeric rating scale 0 to 10 maximum), and frequency (days per month). The analysis was completed on received data only when every effort was made to follow-up participants, even after protocol violation, to minimize potential for bias. Evaluations included were at baseline, 2 weeks (for those in the bariatric surgery arm only), 12 months, and 24 months. The study protocol and statistical analysis plan were published.[21]

Statistical Analysis

Statistical analysis was performed in R v3.6.3 (R Foundation for Statistical Computing, Austria). Data were reported with mean values and SD (median values and ranges for non-normal data) and 95% CIs where appropriate. Missing data were not imputed. Statistical significance was determined by ordinary 1-way analysis of variance with the Tukey multiple comparisons test (mean and SEM). Hierarchical linear regression models were used to analyze repeated measures of the primary and secondary outcomes and estimate differences adjusted for baseline values. In these models, population-level effects (also known as fixed effects) comprised the intercept, time as a factor variable, and the 2-way interaction of treatment arm and time as a factor variable to model changing treatment effects over time. Group-level effects (also known as random effects) comprised patient-level adjustments to the intercept. The threshold for statistical significance was prespecified at $p = 0.05$.

Data Availability

Individual participant data, after anonymization, will be made available, along with the study protocol, statistical analysis plan, and consent forms. On reasonable requests, data beginning at 12 months and ending 3 years after publication of this article will be provided to researchers whose proposed use of the data is approved by the original study chief investigator. Proposals should be made to the corresponding author and requesters will need to sign a data access agreement.

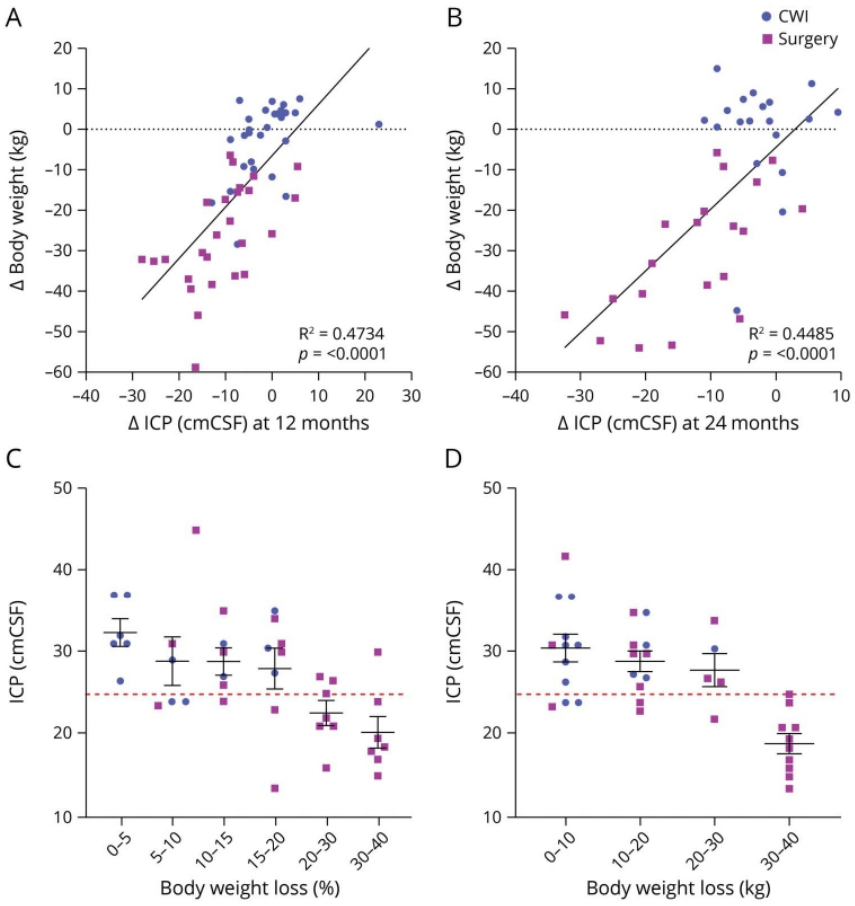
Standard Protocol Approvals, Registrations, and Patient Consents

Ethical permission for the IIH:WT was obtained from the National Research Ethics Committee West Midlands (14/WM/0011). The trial was registered at ClinicalTrials.gov (Identifier: NCT02124486) and ISRCTN (registry number ISRCTN40152829; doi.org/10.1186/ISRCTN40152829). Written informed consent was obtained from all participants. All necessary patient/participant consent has been obtained, and the appropriate institutional forms have been archived.

Results

Sixty-six women were recruited. The study population experienced active disease, as evidenced by the mean ICP of 32.5

Figure 1 Reduced Body Weight Significantly Correlates With Reduced ICP

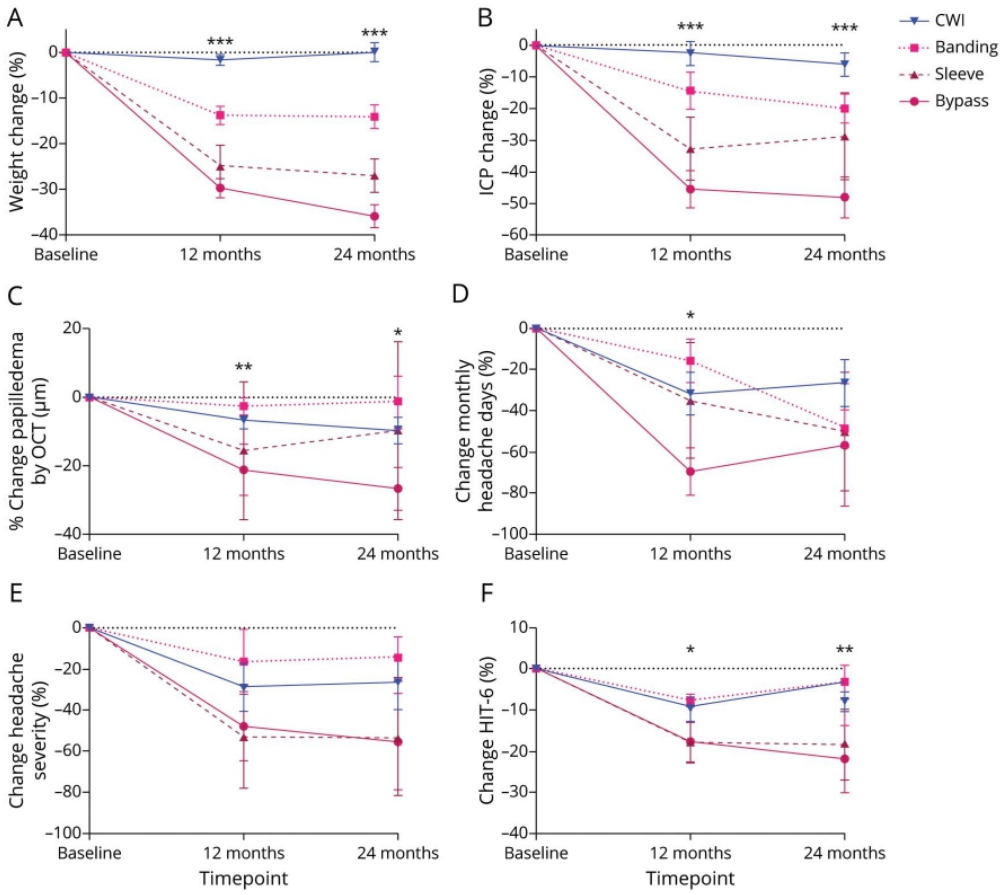


(A, B) Linear regression analysis plotting change in body weight against change in ICP at 12 and 24 months postbaseline. (C, D) ICP levels of patients categorized according to percentage and absolute weight loss at 12 months since baseline measurements. The dashed red line indicates the idiopathic intracranial hypertension diagnostic threshold of an ICP >25 cmCSF. Data presented as mean ± SEM. Statistical significance was determined by ordinary 1-way analysis of variance with the Tukey multiple comparisons test. CWI = community weight management intervention; ICP = intracranial pressure.

(SD 7.8) cmCSF (Table 1). In this planned per-protocol analysis, 20 women who had undergone bariatric surgery were compared at 12 months with 43 who were receiving lifestyle weight management advice (either through WeightWatchers or as part of the bariatric surgery pathway). At baseline, 18 of the 66 were taking acetazolamide; by 12 months, 1 patient in the bariatric surgery arm was still taking 500 mg daily and 8 of the 43 remained on acetazolamide (mean dose 844 mg [SD 498.9]). At both 12 and 24 months, weight and BMI reductions were greater in the bariatric surgery group than in the diet weight management group (eTables 1 and 2, links.lww.com/WNL/C169). For the percentage of weight change and the percentage of excess weight loss, the mean difference (SEM) (95% CI) between those who underwent surgery and those who did not undergo surgery at 12 months was −18.3% (1.9); (−22.1, −14.6), $p <$ 0.001 (Figure 1) and −46.4% (4.9); (−56.1, −36.7), $p < 0.001$, respectively. The 24-month results were similar: −23.6% (2.1); (−27.8, −19.4), $p < 0.001$ and −61.6% (5.5); (−72.3, −50.8), $p <$ 0.001, respectively, with the greatest changes seen in those who underwent bariatric surgery (Figure 1).

Correlation analysis showed that in the total study population, reducing body weight significantly correlated with reducing ICP at both 12 and 24 months ($R^2 = 0.47$, $p < 0.0001$ and $R^2 =$ 0.45, $p < 0.0001$, respectively) (Figure 2, A and B). To further understand this relationship of weight change and ICP levels, weight loss outcomes were summarized by ICP categories (Table 2), and ICP outcomes were summarized by weight loss categories (Table 3). Only those in the bariatric surgery arm managed to achieve sufficient weight loss (in kilograms), which resulted in a fall of ICP below the IIH diagnostic threshold of an ICP ≤25 cmCSF (Figure 2, C and D; Table 3). The mean weight loss required for an ICP ≤25 cmCSF at 12 months was −13.3 kg (1.76) (a 24% decrease in body weight) (Table 2). For ICP to be ≤30 cmCSF, the mean weight loss was −9.94 kg (1.34) (18% decrease in weight) (Figure 2; Table 2). An increased weight loss conferred a proportionally greater drop in ICP (5% weight loss led to a 10% [−4.1 cmCSF] decrease in ICP, 10% weight loss led to a 14% [−4.4 cmCSF] decrease in ICP, and 20% weight loss led to a 26% [−10.2 cmCSF] decrease in ICP) (Table 3).

Figure 2 Surgical Intervention is Significantly More Efficacious at Lowering Body Weight and ICP Than Diet Weight Loss Intervention



Percentage change in diet and surgery groups at baseline, 12-month, and 24-month timepoints for (A) body weight; (B) intracranial pressure; (C) papilledema as measured by OCT volume central thickness; (D) monthly headache days; (E) headache severity; and (F) HIT-6 score; data presented as mean ± SEM. Statistical significance was determined by hierarchical regression modeling in accordance with per-protocol analysis. ***$p < 0.001$. CWI = community weight management intervention; HIT-6 = headache impact test-6; ICP = intracranial pressure; OCT = optical coherence tomography.

The relationship between ICP and weight change was further explored in a hierarchical model to fit the trial outcomes, adjusted for time, intervention, and contemporaneous weight to predict expected ICP values from weight loss. This modeling demonstrated that greater reduction in ICP was predicted with greater weight loss (Figure 3). The effect on ICP further improved between 12 and 24 months as the participants continued to lose weight. For expected ICP values to meet or cross the threshold for normal, at 25cmCSF within 2 years, the model predicted that a patient with a baseline weight of 150 kg would have to have been allocated to the surgery arm and achieved a weight of 110 kg. This predictive modeling showed that those with a higher starting weight needed to lose more weight to meaningfully reduce ICP. This model also demonstrated that among those in the diet arm, if no or little weight loss was achieved in those with a high baseline weight, an increase in ICP would be expected (Figure 3).

Roux-en-Y gastric bypass (RYGB) surgery was the most common surgery performed (n = 13) and proved to be the most successful weight loss method, compared with gastric banding, gastric sleeve, and dietary intervention, recording a reduction at 12 months of −34.9 kg from baseline (adjusted mean difference [95% CI]: −34.9 [−40.0, −29.8]; $p < 0.001$) (eTable 3, links.lww.com/WNL/C169). The effect size increased with a mean of −42.5 kg weight loss between baseline and 24 months (adjusted mean difference [95% CI]: −42.5 [−47.9, −37.1]; $p < 0.001$). (eTable 4) At both 12 and 24 months, the reduction in ICP was greater in the bariatric surgery group than in the diet weight management group ($p < 0.001$) (eTable 5; Figure 1). ICP in the bariatric surgery arm 2 weeks postsurgery showed that the mean ICP (SD) decreased from 34.7 (5.7) cmCSF at baseline to 26.9 (8.1) cmCSF ($p < 0.001$).[22] RYGB recorded the greatest reduction in ICP with the adjusted difference in ICP of −14.4 cmCSF between

Table 2 Absolute Body Weight, Change in Body Weight, and Percentage Change in Body Weight at 12- and 24-Month Time Points Relative to ICP Cutoff Categories

	12-mo posttreatment				24-mo posttreatment			
ICP (cmCSF)	n	Weight (kg, mean ± SEM)	Δ Weight (kg, mean ± SEM)	% Decrease in weight (mean ± SEM)	n	Weight (kg, mean ± SEM)	Δ Weight (kg, mean ± SEM)	% Decrease in weight (mean ± SEM)
≤30	31	96.4 ± 4.92	−9.94 ± 1.34	18.2 ± 2.44	25	90.2 ± 5.56	−23.7 ± 4.04	21.1 ± 3.43
≤25	17	90.2 ± 6.42	−13.3 ± 1.76	24.2 ± 2.59	15	81 ± 5.57	−34.4 ± 4.27	30 ± 3.48
≤20	7	86.2 ± 10.4	−18 ± 2.61	31.2 ± 2.36	6	78.6 ± 10.3	−48 ± 2.72	38.8 ± 2.74

Abbreviation: ICP = intracranial pressure.

baseline and 12 months (adjusted mean difference [95% CI]: −14.4 [−18.1, −10.7]; $p < 0.001$) (eTable 3). ICP at 24 months was recorded to have fallen further (Figure 1B) with the difference between baseline and 24 months with RYGB-adjusted difference of −17.5 (SD 2.0) cmCSF; (adjusted mean difference [95% CI]: −21.4, −13.6; $p < 0.001$) (eTable 3).

Significant reductions in measures of papilledema and headache outcomes were observed with all surgical approaches, with the greatest benefit seen with RYGB (eTable 3, links.lww.com/WNL/C169). RYGB was superior to diet weight management at 12 and 24 months with significant reductions in papilledema, as measured by the optic nerve head volume central thickness, $p < 0.01$ and $p < 0.04$ respectively (eTable 5; Figure 1). There was a significant reduction in monthly headache days at 12 months ($p < 0.05$) (eTable 5; Figure 1), but there was no difference at 12 or 24 months in headache severity score (eTable 5; Figure 1). The percentage change in the headache impact test (HIT)-6 score was significant between the 2 arms at both 12 ($p = 0.019$) and 24 months ($p = 0.003$) (eTable 5; Figure 1).

This study provides CII evidence that weight loss after bariatric surgery results in reduction in intracranial pressure in adult women with idiopathic intracranial hypertension. This study is Class II because of the use of a per-protocol analysis.

Discussion

In this per-protocol analysis of IIH:WT, we have demonstrated the extent of weight loss was directly associated with, and predicted, reduction in ICP. In women with active IIH and a BMI >35 kg/m^2, the amount of weight loss required to normalize the ICP to a level of ≤25 cmCSF was 24% of baseline body weight. To achieve this, it was generally required that the patient be allocated to the bariatric surgery arm. RYGB was the superior procedure for weight loss, ICP reduction, and improvement in both papilledema measures and headache outcomes when compared with the other surgical procedures.

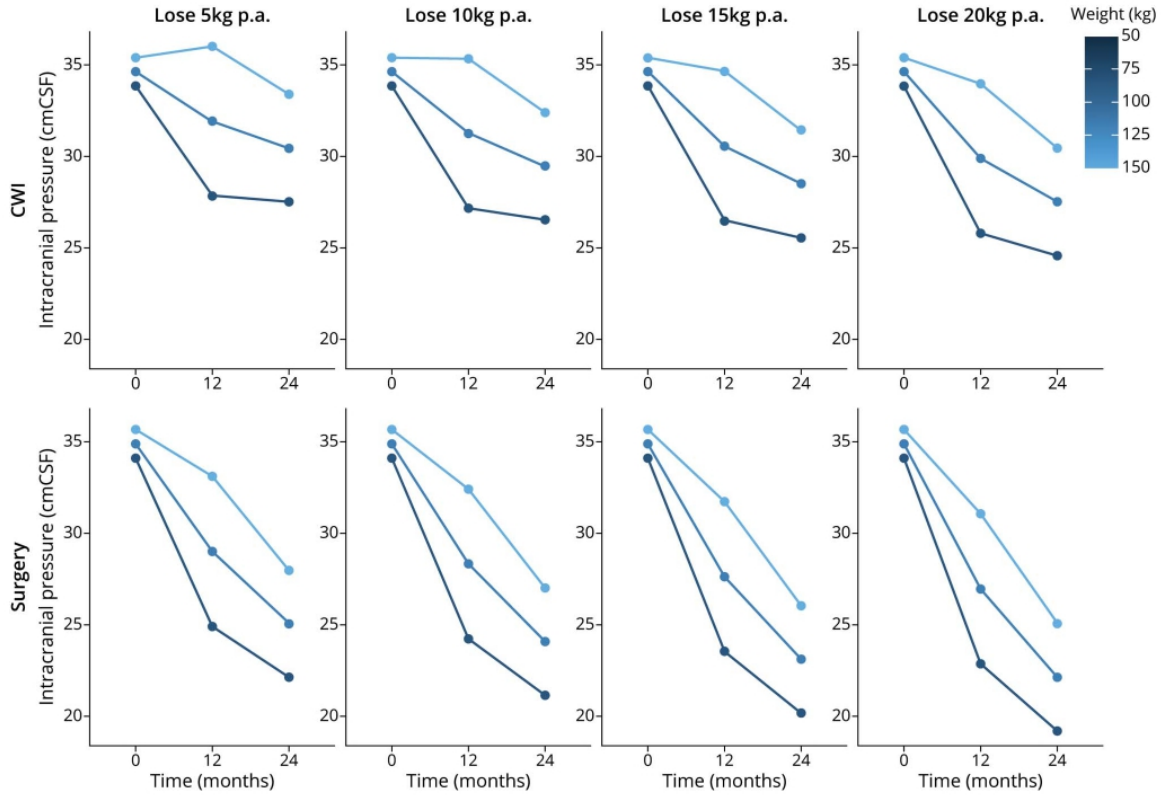
This analysis shows that greater weight loss was associated with greater reductions in ICP, which may not be surprising, considering the previous medical literature linking obesity and IIH.[5,8,9] In a previous study, a very low-energy diet (≤425 kcal/d) for 3 months induced 15% weight loss and lowered ICP significantly (mean 8.0 [SD 4.2] cm CSF, $p < 0.001$). Over the course of the study, improvements in papilledema and visual function and decreased headache frequency and

Table 3 Absolute ICP, Change in ICP, and Percentage Change in ICP at 12 and 24 months Relative to Percentage Weight Loss at 12- and 24-Month Time Points

	12 mo posttreatment			24mo posttreatment		
Weight loss (%)	ICP (cmCSF), mean ± SEM, number	ΔICP (cmCSF), mean ± SEM	% Decrease in ICP (cmCSF), mean ± SEM	ICP (cmCSF, mean ± SEM), number	ΔICP (mmHg, mean ± SEM)	% Decrease in ICP (cmCSF, mean ± SEM)
0–5	32.4 ± 1.65, 6	−4.08 ± 1.66	10.5 ± 4.13	27, 1	—	—
5–10	28.9 ± 2.91, 6	−4.42 ± 2.15	13.6 ± 6.08	29.7 ± 1.67, 6	−3.75 ± 1.63	10.7 ± 4.61
10–15	28.8 ± 1.62, 6	−2.17 ± 2.39	5.79 ± 7.33	—	—	—
15–20	28.1 ± 2.46, 8	−10.2 ± 2.68	26 ± 6.68	28.8 ± 3.68, 4	2.75 ± 3.33	8.68 ± 10.5
20–30	22.6 ± 1.46, 7	−15.4 ± 2.89	39 ± 5.62	20.5 ± 2.51, 6	15.6 ± 2.9	42.6 ± 7.05
30–40	20.3 ± 1.93, 7	−13.6 ± 1.81	39.7 ± 4.59	18.5 ± 1.77, 9	16.1 ± 3.12	44.3 ± 6.81

Abbreviation: ICP = intracranial pressure.

Figure 3 Model-Generated Expected ICP Outcomes for Three Notional Participants With Baseline Weights of 150 kg (Top Line), 120 kg (Middle) and 90 kg (Bottom), Allocated to Each Treatment Arm Under 4 Different Weight Loss Scenarios



The expected ICP values are predicted by a hierarchical model fit to the trial outcomes, adjusted for time, intervention, and contemporaneous weight. CWI = community weight management intervention; ICP = intracranial pressure; p.a. = per annum.

severity with concomitant reduction in analgesic use were noted.[17] However, the amount of weight loss required to normalize ICP (i.e., to a level of or less than 25 cmCSF) had not previously been established. In the IIH:WT, there was a significant difference in the primary outcome of ICP at 12 months in those who underwent bariatric surgery, when compared with the dietary intervention, with an enduring effect at 24 months.[22] When the trial outcomes from all participants were modeled in this study (Figure 3), this demonstrated that greater reduction in ICP was predicted with greater weight loss. Those with a higher starting weight needed to lose more weight to meaningfully reduce ICP. The model demonstrated that in the diet group, if no or little weight loss was achieved in those with a high baseline weight, an increase in ICP would be expected. Therefore, caution should be applied when exposing women with IIH to repeat lifestyle interventions, given the risk of recurrence of their disease and the potential compound effect on repeated episodes of papilledema on the optic nerve health. To cross the ICP lumbar puncture opening pressure threshold of ≤25 cmCSF for all weight loss scenarios, the model predicted that allocation to the bariatric surgery pathway was needed. Hence, clinicians should have low thresholds to refer for bariatric surgery services and not delay weight loss treatment intensification in those who could not achieve adequate weight loss previously or had weight regain. In addition, it is important to consider the effect of weight loss beyond the immediate IIH outcomes. We have shown previously that patients with IIH have an increased risk of cardiovascular disease compared with women with similar BMI.[5] Previous studies showed that bariatric surgery is associated with reduction in CVD and mortality in patients with obesity.[24] This further emphasizes the importance of not delaying bariatric surgery unnecessarily in women with IIH.

Of note was that at 2 weeks postoperatively, there was a significant reduction in ICP. This is consistent with other studies that showed rapid improvements in obesity complications within 3–4 weeks after bariatric surgery, particularly in

type 2 diabetes.[25] There are multiple plausible mechanisms underpinning such quick improvement in ICP including the pre surgical liver shrinkage low-calorie diet, weight loss, and the changes in gut hormones that occur following gastric bypass and sleeve gastrectomy. Our group has previously shown a potential role for GLP-1 receptor agonist in reducing ICP; hence, this could be a possible mechanism in patients who underwent RYGB or sleeve gastrectomy, considering their effect on GLP-1 levels.[24,26,27] The mechanism for this reduction could be debated as an influence of the weight lost in the perioperative period, a direct metabolic effect from gut neuropeptides and their action on the choroid plexus, or a combination of both. What is clear is that for those who require a more expedient reduction in ICP, bariatric surgery could potentially be an acute treatment option for those with IIH in some healthcare settings.[11]

There are several limitations of the analysis, which include the small numbers in each of the bariatric surgery types, and while we have presented the favorable results with RYGB, no specific type of surgery should be recommended over another because this requires further investigation. It may be important to note that those who did not receive surgery had 2 types of weight management programs, one being the weight watchers and the other within the bariatric surgery program, and this could have influenced the results in this group, with the hospital-based weight management program being more structured. In addition, when considering bariatric surgery as a treatment option for IIH, it may not be suitable for everyone. We recommend careful counseling by experts to discuss the side-effect profile, lifelong changes, and the permanent nature of the surgery.

Although bariatric surgery in IIH:WT had high upfront costs,[28] it was more cost-effective with time, both saving money and improving the quality of life at the 5-, 10-, and 15-year time horizons considered.[29] This analysis provides further evidence for considering different types of weight loss methods, supporting bariatric surgery as a management option to be considered in women with active IIH. Bariatric surgery procedures vary in their weight loss outcomes their effect on obesity complications and weight loss. Unfortunately, our study was limited by being too small to determine which procedure is best for women with IIH. However, our findings that RYGB resulted in greater weight loss are consistent with the literature.[30] The choice of which procedure to perform should be based on a shared decision-making process between the patient and the surgeon, considering the potential benefits, harms, and complications if any are present.

In women with active IIH and a BMI >35 kg/m^2, the amount of weight loss required to normalize the ICP to a level of ≤25 cmCSF is 24% of baseline body weight. This is unlikely to be achieved by dietary interventions alone, and early referral to a bariatric surgical pathway should be considered.

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Disclosure

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Continued

Appendix *(continued)*

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Appendix *(continued)*

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eTable 1: Results at 12 months follow-up

12 months mean (SD), number					
	Bariatric surgery				Diet weight management
	All	RYGB	LGB	LSG	
Intracranial pressure (cmCSF)	24.3 (9.4), 19	20.4 (4.7), 12	40.3 (12.1), 3	23.9 (5.4), 4	31.5 (5.3), 35
Weight (kg)	91.0 (26.3), 20	81.2 (20.8), 12	125.5 (25.0), 4	85.8 (12.8), 4	112.4 (22.1), 39
Excess body weight (Kg)	24.6 (24.7), 20	15.5 (20.9), 12	56.7 (21.8), 4	19.6 (7.2), 4	44.8 (21.3), 39
Body mass index (kg/m^2)	34.2 (8.8), 20	31.0 (7.8), 12	45.3 (6.9), 4	32.3 (2.4), 4	41.5 (7.9), 39
OCT global peripapillary retinal nerve fiber layer thickness worse eye (µm)	104.0 (31.1), 20	97.1 (11.3), 12	105.2 (30.6), 4	123.8 (63.2), 4	109.1 (30.2), 37
OCT optic nerve head volume central thickness worse eye (µm)	501.2 (179.7), 17	455.6 (107.5), 11	580.5 (376.9), 2	587.0 (254.3), 4	578.4 (126.6), 36
Perimetric mean deviation worst eye (dB)	-2.8 (2.8), 19	-2.3 (2.1), 11	-2.5 (3.0), 4	-4.6 (4.1), 4	-2.2 (2.3), 39
Monthly headache days	10.8 (12.1), 20	9.3 (11.1), 12	13.0 (15.1), 4	13.0 (15.1), 4	17.2 (10.8), 33
Headache severity (VRS 0-10)	2.7 (2.7), 20	2.7 (2.7), 12	3.3 (3.9), 4	1.9 (2.2), 4	4.1 (3.0), 33
HIT-6 score	55.2 (9.8), 19	51.7 (9.1), 11	63.8 (4.9), 4	56.2 (11.4), 4	60.3 (10.9), 36

eTable 2: Results at 24 months follow-up

24 months mean (SD), number					
	Bariatric surgery				Diet weight management
	All	RYGB	LGB	LSG	
Intracranial pressure (cmCSF)	20.4 (7.8), 15	17.0 (4.5), 10	35.0 (-), 1	25.5 (8.8), 4	30.1 (5.6), 25
Weight (kg)	83.2 (27.6), 16	72.5 (18.8), 10	137.5 (32.2), 2	83.0 (7.5), 4	112.1 (22.8), 30
Excess body weight (Kg)	16.3 (26.5), 16	6.0 (19.9), 10	66.1 (31.0), 2	16.9 (1.4), 4	44.5 (22.6), 30
Body mass index (kg/m^2)	31.0 (9.4), 16	27.5 (7.5), 10	48.0 (10.5), 2	31.3 (0.4), 4	41.5 (8.4), 30
OCT global peripapillary retinal nerve fiber layer thickness worse eye (µm)	98.1 (31.3), 14	92.8 (13.1), 8	81.5 (44.5), 2	117.0 (49.5), 4	108.5 (28.4), 30
OCT optic nerve head volume central thickness worse eye (µm)	469.8 (182.9), 13	445.3 (106.8), 7	314.0 (91.9), 2	590.8 (266.8), 4	544.4 (135.6), 28
Perimetric mean deviation worst eye (dB)	-2.5 (2.4), 16	-2.1 (1.8), 10	-2.0 (2.1), 2	-3.6 (3.8), 4	-1.9 (2.6), 30
Monthly headache days	11.0 (13.2), 16	8.8 (12.5), 10	16.0 (17.0), 2	14.0 (16.2), 4	15.2 (10.4), 29
Headache severity (VRS 0-10)	3.3 (3.5), 16	2.9 (3.6), 10	7.3 (0.4), 2	2.2 (2.9), 4	4.1 (2.8), 29
HIT-6 score	52.7 (13.6), 15	49.2 (14.2), 9	61.0 (8.5), 2	56.2 (14.4), 4	61.1 (10.3), 31

HIT-6 = headache impact test-6 ICP = intracranial pressure; IIH:WT = idiopathic intracranial hypertension weight trial; LSG - laparoscopic sleeve gastrectomy; LGB - laparoscopic gastric band; OCT = optical coherence tomography; RYGB - Roux-en-Y gastric bypass; SD = standard deviation; VRS = verbal rating scale

eTable 3: Difference between baseline and 12 months using hierarchical regression analysis.

Difference between baseline and 12 months Hierarchical regression mean (SE); 95%CI, p				
	RYGB	LGB	LSG	Diet weight management
Intracranial pressure (cmCSF)	-14.4 (1.9); (-18.1, -10.7), p<0.001	7.1 (3.5); (0.3, 14.0), p=0.044	-12.4 (3.3); (-18.9, -5.9), p<0.001	-3.3 (1.1); (-5.4, -1.2), p=0.003
Weight (kg)	-34.9 (2.6); (-40.0, -29.8), p<0.001	-1.8 (4.4); (-10.4, 6.8), p=0.683	-29.4 (4.6); (-38.4, -20.5), p<0.001	-5.6 (1.5); (-8.4, -2.7), p<0.001
Excess body weight (Kg)	-34.2 (2.6); (-39.3, -29.1), p<0.001	-1.7 (4.4); (-10.3, 6.9), p=0.699	-29.2 (4.6); (-38.1, -20.3), p<0.001	-5.4 (1.4); (-8.3, -2.6), p<0.001
Body mass index (kg/m^2)	-12.7 (1.0); (-14.6, -10.8), p<0.001	-0.6 (1.6); (-3.8, 2.5), p=0.688	-10.8 (1.7); (-14.1, -7.5), p<0.001	-2.0 (0.5); (-3.0, -0.9), p<0.001
OCT global peripapillary retinal nerve fiber layer thickness worse eye (µm)	-76.7 (25.0); (-125.6, -27.8), p=0.003	-19.6 (40.0); (-98.0, 58.8), p=0.625	-7.7 (43.2); (-92.5, 77.0), p=0.858	-47.3 (13.9); (-74.5, -20.2), p=0.001
OCT optic nerve head volume central thickness worse eye (µm)	-148.5 (48.9); (-244.3, -52.8), p=0.003	-61.4 (91.0); (-239.7, 117.0), p=0.502	-169.5 (68.8); (-304.3, -34.7), p=0.016	-53.2 (25.1); (-102.5, -4.0), p=0.037
Perimetric mean deviation worst eye (dB)	1.3 (0.8); (-0.3, 3.0), p=0.121	-0.6 (1.4); (-3.3, 2.1), p=0.649	1.2 (1.4); (-1.6, 4.0), p=0.409	1.3 (0.5); (0.4, 2.2), p=0.005
Monthly headache days	-12.8 (3.1); (-18.8, -6.7), p<0.001	-2.6 (5.6); (-13.6, 8.3), p=0.640	-9.0 (5.4); (-19.7, 1.7), p=0.102	-5.6 (1.8); (-9.3, -2.0), p=0.003
Headache severity (VRS 0-10)	-2.6 (0.9); (-4.3, -0.9), p=0.003	0.0 (1.5); (-3.0, 2.9), p=0.980	-2.5 (1.5); (-5.4, 0.5), p=0.107	-1.0 (0.5); (-2.0, 0.0), p=0.045
HIT-6 score	-11.7 (2.9); (-17.4, -6.1), p<0.001	2.1 (4.7); (-7.0, 11.3), p=0.652	-12.0 (4.9); (-21.6, -2.4), p=0.016	-5.3 (1.6); (-8.4, -2.2), p=0.001

eTable 4: Difference between baseline and 24 months using hierarchical regression analysis.

Difference between baseline and 24 months Hierarchical regression mean (SE); 95%CI, p				
	RYGB	LGB	LSG	Diet weight management
Intracranial pressure (cmCSF)	-17.5 (2.0); (-21.4, -13.6), p<0.001	-0.7 (5.6); (-11.6, 10.2), p=0.901	-10.8 (3.3); (-17.2, -4.3), p=0.002	-4.7 (1.2); (-7.1, -2.3), p<0.001
Weight (kg)	-42.5 (2.8); (-47.9, -37.1), p<0.001	1.0 (5.7); (-10.3, 12.2), p=0.868	-32.2 (4.6); (-41.2, -23.3), p<0.001	-5.2 (1.6); (-8.3, -2.1), p=0.001
Excess body weight (Kg)	-42.8 (2.8); (-48.2, -37.4), p<0.001	0.4 (5.7); (-10.8, 11.6), p=0.948	-31.9 (4.6); (-40.8, -23.0), p<0.001	-5.2 (1.6); (-8.3, -2.1), p=0.001
Body mass index (kg/m^2)	-16.0 (1.0); (-18.0, -14.0), p<0.001	0.0 (2.1); (-4.2, 4.1), p=0.985	-11.8 (1.7); (-15.1, -8.5), p<0.001	-1.8 (0.6); (-2.9, -0.6), p=0.002
OCT global peripapillary retinal nerve fiber layer thickness worse eye (μm)	-84.1 (28.2); (-139.5, -28.8), p=0.004	-41.0 (51.5); (-141.8, 59.9), p=0.427	-14.5 (43.2); (-99.2, 70.2), p=0.738	-47.2 (14.8); (-76.2, -18.2), p=0.002
OCT optic nerve head volume central thickness worse eye (μm)	-170.1 (54.9); (-277.8, -62.4), p=0.003	-206.2 (91.0); (-384.5, -27.8), p=0.026	-165.7 (68.8); (-300.6, -30.9), p=0.018	-76.3 (27.4); (-130.0, -22.5), p=0.007
Perimetric mean deviation worst eye (dB)	1.7 (0.9); (0.0, 3.5), p=0.048	0.5 (1.8); (-3.0, 4.1), p=0.767	2.2 (1.4); (-0.6, 5.0), p=0.123	1.7 (0.5); (0.7, 2.6), p=0.001
Monthly headache days	-12.8 (3.3); (-19.2, -6.3), p<0.001	1.5 (6.9); (-12.1, 15.0), p=0.832	-8.0 (5.4); (-18.7, 2.7), p=0.145	-8.2 (1.9); (-12.0, -4.4), p<0.001
Headache severity (VRS 0-10)	-2.4 (0.9); (-4.2, -0.6), p=0.010	4.1 (1.9); (0.4, 7.8), p=0.031	-2.1 (1.5); (-5.1, 0.8), p=0.164	-1.3 (0.5); (-2.3, -0.2), p=0.018
HIT-6 score	-14.2 (3.1); (-20.3, -8.1), p<0.001	1.7 (6.1); (-10.4, 13.7), p=0.786	-12.0 (4.9); (-21.6, -2.4), p=0.016	-4.9 (1.7); (-8.2, -1.6), p=0.004

HIT-6 = headache impact test-6 ICP = intracranial pressure; IIH:WT = idiopathic intracranial hypertension weight trial; LSG - laparoscopic sleeve gastrectomy; LGB - laparoscopic gastric band; OCT = optical coherence tomography; RYGB - Roux-en-Y gastric bypass; SD = standard deviation; VRS = verbal rating scale.

eTable 5: The difference between Roux-en-Y gastric bypass (RYGB) and weight management intervention at 12 months and 24 months using a hierarchical regression analysis.

Difference between Roux-en-Y gastric bypass and diet weight management intervention Hierarchical regression mean (SE); 95%CI, p		
	12 months	24 months
Intracranial pressure (cmCSF)	-11.5 (2.0); (-15.3, -7.6), p<0.001	-13.2 (2.2); (-17.4, -9.0), p<0.001
Weight (kg)	-27.6 (6.8); (-40.9, -14.4), p<0.001	-35.6 (6.9); (-49.0, -22.1), p<0.001
Excess body weight (Kg)	-25.8 (6.4); (-38.3, -13.2), p<0.001	-34.6 (6.5); (-47.4, -21.9), p<0.001
Body mass index (kg/m^2)	-9.2 (2.3); (-13.8, -4.7), p<0.001	-12.7 (2.4); (-17.4, -8.1), p<0.001
OCT global peripapillary retinal nerve fiber layer worse eye (μm)	-12.1 (21.9); (-55.0, 30.8), p=0.580	-19.7 (26.1); (-70.8, 31.4), p=0.450
OCT optic nerve head volume central thickness worse eye (μm)	-125.2 (53.2); (-229.3, -21.0), p=0.019	-123.7 (60.6); (-242.6, -4.9), p=0.041
Perimetric mean deviation worst eye (dB)	0.2 (1.0); (-1.8, 2.2), p=0.845	0.3 (1.0); (-1.8, 2.3), p=0.801
Monthly headache days	-7.8 (3.4); (-14.4, -1.1), p=0.023	-5.2 (3.6); (-12.3, 1.9), p=0.153
Headache severity (VRS 0-10)	-1.5 (0.9); (-3.2, 0.2), p=0.090	-1.0 (0.9); (-2.9, 0.8), p=0.275
HIT-6 score	-7.6 (3.3); (-14.1, -1.2), p=0.019	-10.5 (3.5); (-17.4, -3.6), p=0.003

HIT-6 = headache impact test-6 ICP = intracranial pressure; IIH:WT = idiopathic intracranial hypertension weight trial; LSG - laparoscopic sleeve gastrectomy; LGB - laparoscopic gastric band; OCT = optical coherence tomography; RYGB - Roux-en-Y gastric bypass; SD = standard deviation; VRS = verbal rating scale.

Publication 7: Intracranial pressure directly predicts headache morbidity in idiopathic intracranial hypertension

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Intracranial pressure directly predicts headache morbidity in idiopathic intracranial hypertension

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Abstract

Objective: Headache is the predominant disabler in idiopathic intracranial hypertension (IIH). The aim was to characterise headache and investigate the association with intracranial pressure.

Methods: IIH:WT was a randomised controlled parallel group multicentre trial in the United Kingdom investigating weight management methods in IIH. Participants with active IIH (evidenced by papilloedema) and a body mass index (BMI) ≥35 kg/m^2 were recruited. At baseline, 12 months and 24 months headache characteristics and quality of life outcome measures were collected and lumbar puncture measurements were performed.

Results: Sixty-six women with active IIH were included with a mean age of 32.0 years (SD ± 7.8), and mean body mass index of 43.9 ± 7.0 kg/m^2. The headache phenotype was migraine-like in 90%. Headache severity correlated with ICP at baseline ($r = 0.285$; $p = 0.024$); change in headache severity and monthly headache days correlated with change in ICP at 12 months ($r = 0.454$, $p = 0.001$ and $r = 0.419$, $p = 0.002$ respectively). Cutaneous allodynia was significantly correlated with ICP at 12 months. ($r = 0.479$, $p < 0.001$). Boot strap analysis noted a positive association between ICP at 12 and 24 months and enabled prediction of both change in headache severity and monthly headache days. ICP was associated with significant improvements in quality of life (SF-36).

Conclusions: We demonstrate a positive relationship between ICP and headache and cutaneous allodynia, which has not been previously reported in IIH. Those with the greatest reduction in ICP over 12 months had the greatest reduction in headache frequency and severity; this was associated with improvement of quality of life measures.

Trial registration: This work provides Class IIa evidence of the association of raised intracranial pressure and headache. ClinicalTrials.gov number, NCT02124486.

Keywords: Idiopathic intracranial hypertension, Migraine, Intracranial pressure, Allodynia, Calcitonin gene related peptide

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Introduction

Idiopathic intracranial hypertension (IIH) is a rare disease that is increasingly recognised [1, 2]. It is characterized by raised intracranial pressure (ICP) in the absence of a structural cause on brain imaging [3, 4]. Although the exact cause of IIH remains unknown, disease development is associated with obesity and there is increasing evidence to suggest adipose dysfunction [5]. Headache is the predominant symptom and is prioritized highly by patients and physicians [6]. The headache in IIH remains under-characterized [7] and is associated with significant morbidity and reduced quality of life [8].

The International Classification of Headache Disorders (ICHD-3 beta) attributes headache in IIH to be associated with raised intracranial pressure and acknowledges that it often mimics primary headache disorders such as migraine [9]. While the International Headache Society stipulates the importance on relief of headache following removal of cerebrospinal fluid (CSF), evidence suggests this relief is far from universal [10] and can occur due to co-occurring headache disorders such as migraine [11]. Rarely some patients with evidence of raised ICP do not ever develop headache [12]. The pathogenesis of IIH headache remains unknown, as do the risk factors that propagate persistent headache. Calcitonin gene-related peptide (CGRP) monoclonal antibodies have been noted in a prospective study to significantly improve headache in patients with IIH and persistent post-IIH headache (resolved papilloedema), suggesting CGRP may modulate headache pain [13, 14].

The relationship between development of headache and raised ICP in IIH is poorly understood. A previous trial in 165 patients with newly diagnosed IIH [15] did not identify an association between intracranial pressure and headache. However, a question remains as to whether the role of ICP in driving ongoing headache in patients with chronic headache.

The aim of this analysis was to describe the headache characteristics in those with active IIH recruited to the multicentre IIH Weight Trial (IIH:WT), and to explore the relationship of headache features to ICP.

Methods

Study procedures

Between July 25, 2014 and May 25, 2017, 66 female patients were recruited to the multicentre randomised controlled trial IIH:WT, comparing the efficacy of a bariatric surgery pathway versus the dietary intervention Weight Watchers™. All participants had active IIH with papilloedema and lumbar puncture opening pressures ≥25 cm cerebrospinal fluid, in accordance with agreed criteria for diagnosis of IIH [1]. The protocol and eligibility criteria have been previously published [16].

At baseline a detailed clinical, medication and standardized headache history was taken (including the location, character, associated symptoms, timing and exacerbating / relieving factors) by a physician with specialist training in headache phenotyping. Headache preventatives were permitted during the study, but any changes were recorded. As part of the trial anthropometric data including weight and height were recorded, and a lumbar puncture was performed. Headaches were characterized using ICHD-3beta criteria for primary and secondary headache disorders [9].

At baseline, 12 and 24 months all IIH patients were required to return a headache diary which included details of headache severity; headache duration; headache frequency (monthly headache days); and analgesic use (days per month). The headache severity was scored using a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (the most severe pain level experienced by the subject). The NRS is favoured by patients and widely used in migraine trials [17].

Cutaneous allodynia symptoms were assessed during a headache using the patient-completed Allodynia Symptom Checklist-12 (ASC-12) in the week prior to their baseline and 12 month visit. Score ranges from 0 = no symptoms to 24 = severe symptoms; 0–2 = no allodynia, 3–5 = mild allodynia, 6–8 = moderate allodynia, 9 or more = severe allodynia (supplemental methods). In addition, pressure allodynia was assessed in patients at baseline and at 12 months using three different weights of von Frey hairs (F1, 0.32 g; F2, 8.30 g; and F3, 24 g) over V1–3 and C2–3 dermatomes bilaterally [18]. Patients rated pressure allodynia using a 100 mm visual analogue scale.

Outcome measures included the headache impact test-6 disability questionnaire (HIT-6); where little or no impact = HIT-6 score ≤ 49; some impact = HIT-6 score 50–55; substantial impact = HIT-6 score 56–59; severe impact = HIT-6 score ≥ 60. Health-related quality of life was assessed using the Rand patient-reported 36-Item Short Form Health Survey (SF-36). The eight sections of the SF-36 yielded two summary scores (physical component summary, PCS; and mental component summary, MCS).

Statistical analysis

Descriptive statistics were used to compare demographic characteristics. Analysis by trial arm was not part of the aims of the study. Statistical analysis was performed using GraphPad, version 8.3 (GraphPad Software, La Jolla, California, USA). Mean and standard deviations are provided for normally distributed variables, and median and range provided for non-normally distributed variables. Pearson's correlation coefficient was computed where the variables were

normally distributed and all assumptions were met, with Spearman's rank correlation used in other cases. Values were deemed statistically significant at $p < 0.05$. Missing data, due to any absence or choice, were excluded from the analysis and not imputed.

Hierarchical regression models were generated, with data for all patients analysed in one model. Models contained population-level terms (i.e. terms that apply to each experimental unit) to reflect: 1) the mean baseline value (i.e. the intercept); 2) the mean change from baseline associated with each assessment time (i.e. time as a factor variable); 3) the extra mean change from baseline associated with each assessment time in the experimental arm (i.e. the interaction of treatment allocation and time as a factor variable). Additionally, hierarchical regression models contained random effects (i.e. terms that are specific to each experimental unit) to reflect the random deviations from the population-level mean value at baseline (i.e. random intercepts). For ICP, the random intercepts were estimated for each patient, with each of these parameters assumed to be exchangeable draws from a normal distribution.

To assess the relationship between ICP and headache, we have bootstrap resampling of the observed outcomes to generate alternative pairs of treatment effects. Alternative datasets were generated by resampling patients with replacement from the original treatment allocations to which they were randomised. The hierarchical regression model described above was fitted to each resampled dataset, producing a pair of treatment effects for the surrogate and clinical outcomes from a notional randomisation of patients. This process was repeated 1000 times. The resampled datasets within in each arm in each trial were the same size as the original datasets.

Standard protocol approvals, registration, and patient consent

The trial was approved by The National Research Ethics Committee West Midlands – The Black Country, on 28 February 2014 (14/WM/0011). All participants gave written consent after receiving detailed written information. The trial was registered, clinicaltrials.gov identifier: NCT02124486.

Data availability statement

Anonymised individual participant data will be made available along with the trial protocol and statistical analysis plan. Proposals should be made to the corresponding author and will be reviewed by the Birmingham Clinical Trials Unit Data Sharing Committee in discussion with the Chief Investigator. A formal Data Sharing Agreement may be required between respective organisations once release of the data is approved and before data can be released.

Classification of evidence

This work provides Class IIa evidence that headache is associated with intracranial pressure.

Results

Patient characteristics

Sixty-six persons (100% women) with active IIH were included in the analysis (Table 1). Mean age at inclusion was 32.0 years (SD ±7.8, range 20–53 years), and the mean body mass index was $43.9 \pm 7.0\,kg/m^2$ ranging from 35.3 to $63.3\,kg/m^2$. The median IIH disease duration was 1.1 years (IQR 0.5–2.6) and ranging from 0.1 to 20.0 years. Forty-five participants (68%) reported a previous history of migraine, of which 24 (53%) reported onset in childhood (age < 18 years).

Table 1 Characteristics of the study cohort at baseline

	Total ($n = 66$)
Age in years, mean (SD)	32 (7.8)
Ethnicity, number (%)	
White	55 (83)
Mixed	5 (8)
Asian	1 (1)
Black	5 (8)
Duration of IIH diagnosis, median (IQR)	1.1 (0.5–2.6)
Number on acetazolamide (%)	19 (29)
Number on topiramate (%)	6 (9)
Lumbar puncture opening pressure, cmCSF, mean (SD)	35.5 (7.0)
Weight, Kg (SD)	118.5 (21.1)
Body Mass Index (weight (kg)/ height (m^2), mean (SD)	43.9 (7.0)
Smoking status - smoker	$n = 27$
Smoking intensity of 10 or more cigarettes per day, n (%)	18 (67)
Family history of primary headache disorder, %	19 (7/37)
Previous history of migraine, n (%)	45 (68)
Duration of migraine, n (%)	$n = 45$
Less than 1 year	5 (11)
1–5 years	7 (16)
5–10 years	5 (11)
10–20 years	3 (7)
More than 20 years	1 (2)
Since childhood (age < 18 years)	24 (53)
Headache preventative medication use, n (%)	$n = 18$
Beta-blocker	1 (6)
Tricyclic antidepressant	7 (39)
Anticonvulsant	8 (44)
Other	2 (11)

Headache characteristics at baseline

Within this cohort 65 participants (98%) reported headache at the time of their IIH diagnosis. At the time of the baseline assessment 63 (95%) reported headache. In some cases patients described more than one type of headache. The headache phenotype was migraine-like in 57 of 63 (90%) and of those, 23 (40%) described migraine aura. Of those with migraine-like headaches 40 (70%) had a phenotype consistent with chronic migraine-like headaches (> 15 headache days per month of which > 8 are migraine-like), while 17 (30%) had episodic migraine-like headaches (less than 15 headache days per month) [8]. At the time of study assessment, 44 (67%) had headache, which fulfilled the diagnostic criteria for headaches attributed to IIH. 23 (35%) patients fulfilled the criteria for medication-overuse headaches. There was one patient who had headaches not attributable to either migraine-like or attributable to IIH, and had tension-type headache.

Headache location was predominately bilateral 76%; with fewer reporting unilateral pain, 20% being on the right side and 18% being on the left side (note these were not mutually exclusive responses, Supplemental Table 1). Headache pain was typically throbbing 73%, but also a pressure sensation 55% and less commonly stabbing 11% or shooting 7%. Photophobia and phonophobia were described in 81% and 60%, respectively, with fewer (19%) describing osmophobia. 70% described nausea and 18% experienced vomiting with their headache attacks. Dizziness was reported in 33%. Headaches on waking were reported in 12%. Autonomic features were rarely reported 5%. Pulsatile tinnitus was a feature in 74%. Headaches were exacerbated by physical activity in 53%; by lying flat in 32%; on bending 31%; and on Valsalva manoeuvre in 23%. (Table 3).

Headache burden

Headache disability, as measured by the Headache Impact Test (HIT-6) questionnaire, had a mean score of 65 (SD ±7.3) at baseline. Mean headache severity was 5.0 (SD ±2.0) and mean daily duration of headache was 8.2 h (SD ±6.3). Monthly headache days were mean 22.2 days (SD ±7.8) and mean monthly analgesic use was 12.3 days (9.0).

By 12 months 76% of participants reported ongoing headache. The mean headache severity had improved (3.6 (SD ±2.9), with a concurrent reduction in the headache frequency (monthly headache days 15.1 (SD ±11.5)) and monthly analgesic use (8.6 (SD ±9.8)). No parameter reached statistical significance.

Medications at baseline

At baseline 38% participants were receiving medication specifically to lower ICP. This included 29% receiving Acetazolamide, and 9% Topiramate. 5% of participants were receiving diuretics (Bendroflumethiazide, $n = 1$; Furosemide, $n = 1$; and Co-amilofruse, $n = 1$). 27% of participants were receiving medication for prevention of headache (migraine and/or tension-type headache) (beta blocker, $n = 1$; tricyclic antidepressant, $n = 7$; anticonvulsant, $n = 8$; other, $n = 2$) (Table 2).

Relationship of ICP to headache

The whole cohort mean lumbar puncture opening pressure (LP OP) at baseline was 34.7cmCSF (SD 5.7) which reduced to 28.95 (SD 7.7) and 26.8 (SD 8.0) by 12 and 24 months respectively. Headache severity at baseline correlated with ICP (Fig. 1a, $r = 0.285$, $p = 0.024$) although the monthly headache days did not. The reduction in ICP over 12 months correlated with the reduction in headache severity and monthly headache days (MHD) (Fig. 1b and c, $r = 0.454$, $p = 0.001$ and $r = 0.419$, $p = 0.002$ respectively). This relationship continued at 24 months but did not reach statistical significance.

Table 2 Outcome measures, headache phenotype and ictal cutaneous allodynia at baseline

Headache at baseline, n (%)	63 (95%)
Headache severity, verbal rating scale (0–10), mean (SD)	5.0 (2.0)
Headache duration (hours), mean (SD)	8.2 (6.3)
Headache frequency (days per month), mean (SD)	22.2 (7.8)
Analgesic use (days per month), mean (SD)	12.3 (9.0)
HIT-6 score, mean (SD)	65 (7.3)
SF-36, physical component score, mean (SD) $n = 60$	28.7 (12.7)
SF-36, mental component score, mean (SD) $n = 60$	37.7 (11.0)
Headache phenotypes (not mutually exclusive), n (%)	$n = 66$
No headache	1 (2%)
Migraine-like	57 (86%)
Migraine-like without aura	34 (60%)
Migraine-like with aura	23 (40%)
Chronic migraine-like	40 (70%)
Episodic migraine-like	17 (30%)
Headache attributed to IIH	44 (67%)
Medication-overuse	23 (35%)
Tension-like	1 (2%)
Cutaneous allodynia (ictal), mean (SD), $n = 58$	19.16 (5.79)
None (0–2)	0 (0%)
Mild (3–5)	0 (0%)
Moderate (6–8)	2 (3.4%)
Severe (9+)	56 (96.6%)

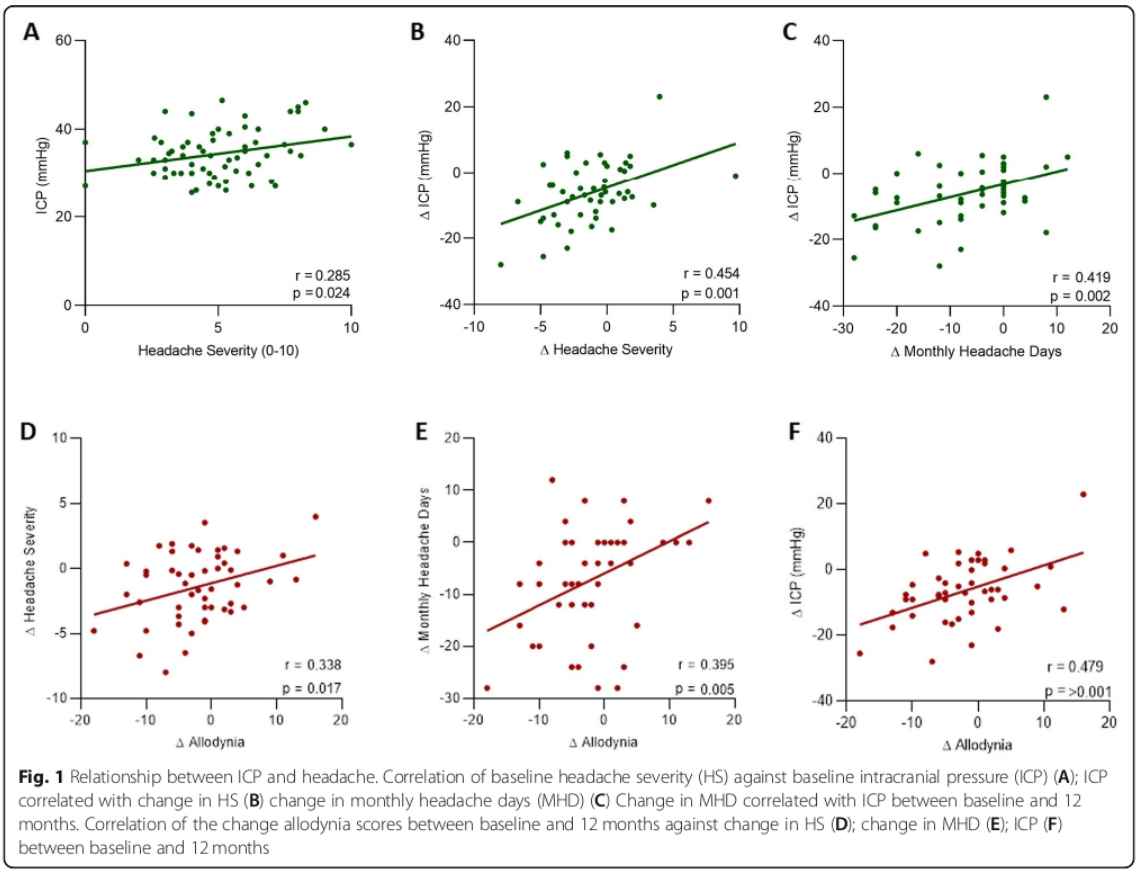

Fig. 1 Relationship between ICP and headache. Correlation of baseline headache severity (HS) against baseline intracranial pressure (ICP) (**A**); ICP correlated with change in HS (**B**) change in monthly headache days (MHD) (**C**) Change in MHD correlated with ICP between baseline and 12 months. Correlation of the change allodynia scores between baseline and 12 months against change in HS (**D**); change in MHD (**E**); ICP (**F**) between baseline and 12 months

Relationship between cutaneous allodynia and ICP

At baseline 58/63 (92%) reported ictal cutaneous allodynia with a mean cutaneous allodynia score of 19.2 (SD ± 5.79) and reducing at 12 months to a mean of 17.1 (SD ± 7.20) ($p = 0.01$). There was no relationship between the allodynia score and headache severity and MHD at baseline. By 12 month MHD correlated with the allodynia score ($r = 0.331$, $p = 0.015$). The change in MHD and headache severity over 12 months correlated with the improving allodynia score (Fig. 1d and e, $r = 0.395$, $p = 0.005$ and $r = 0.338$, $p = 0.017$ respectively). The change in allodynia over 12 months also correlated with the change in ICP (Fig. 1e, $r = 0.479$, $p < 0.001$). There was no relationship between body mass index (BMI) and allodynia. Pressure allodynia did not change significantly between baseline and 12 months and was not associated with headache severity, MHD or ICP (Supplemental Table 2).

Predicting the effects of ICP on headache outcomes

Analysis identified a positive association between ICP and headache severity and MHD at 12 and 24 months, with a larger change in intracranial pressure coinciding with a larger change in headache measures (Fig. 2a). The bootstrapped analysis data points (Fig. 2) represent trial outcomes, each as likely as any other. Thus the location and dispersion of the points provides evidence on the coincident nature of the change in intracranial pressure. Predictability was observed at all time points (12 and 24 months). Utilizing the surrogacy analysis plots (Fig. 2), changes in headache measures can be inferred from changes in ICP (Table 3) e.g. at 12 months follow up the reduction in ICP of − 5 cmCSF is associated with a change in headache severity of − 0.95 and a mean MHD of − 3.06. Whereas a reduction in ICP of − 10 cmCSF was associated with a reduction of headache severity of − 1.35 and mean MHD of − 4.08, at 12 months (Table 3).

Quality of life and intracranial pressure

Quality of life, as measured by SF-36 PCS and MCS were 28.7 (12.7) and 37.7 (11.0) respectively at baseline and 37.7 (14.9) and 38.9 (12.2) respectively by 12 months (Table 2). There was no relationship between SF-36 scores and headache severity, MHD and ICP at baseline.

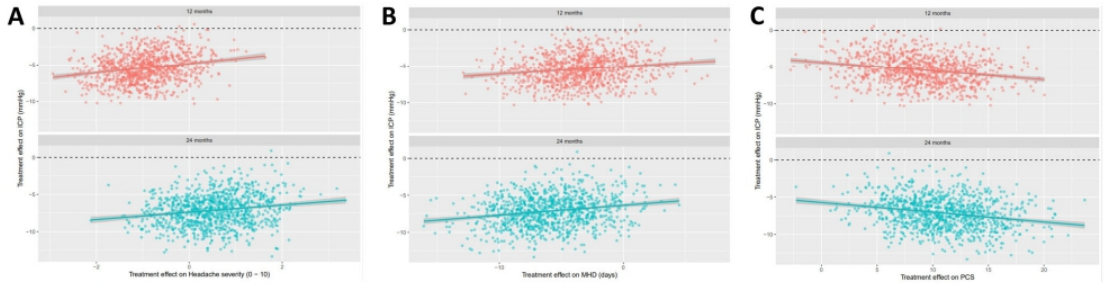

Fig. 2 Bootstrap surrogacy analysis of ICP and headache outcomes. The x-axis reflects change in headache outcomes with change in ICP on the y-axis. The lines are simple linear regressions and the shaded regions are 95% confidence intervals of the mean. Changes in intracranial pressure are plotted at 12 and 24 months. Each positive value represent improvement i.e. reduction in ICP and headaches outcomes, with the larger the angle of the slope the greater the relationship. **A** Illustrates headache severity on the y axis with a positive association with ICP over the time horizons. **B** Illustrates monthly headache days (MHD) on the y axis with a positive association with ICP over the time horizons. **C** Illustrates quality of life physical component score (PCS) on the y axis with a positive association with ICP over the time horizons

The improvement in the PCS was associated with improving headache severity at 12 and 24 months (Fig. 3a and b, $r = -0.522$, $p < 0.001$ and $r = -0.356$, $p = 0.04$, respectively). The PCS also improved in association with reduction in ICP at 12 months ($r = -0.546$, $p < 0.001$). MCS did not relate to headache or ICP. Analysis identified a positive association between ICP and PCS at 12 and 24 months (Fig. 3C).

Subanalysis by treatment assignment and disease duration was not possible due to small numbers in each group.

Discussion

Headache is a near universal sequela of IIH, and can complicate other disorders with raised ICP. We demonstrate a positive relationship between ICP and headache severity and monthly headache days, which has not been noted previously in IIH. Patients with the greatest reduction in ICP over 12 months saw the greatest reduction in headache frequency and severity, and this was associated with improvement of physical functioning in the quality of life SF-36.

We observed that the majority of patients with IIH had migraine-like headaches at baseline, as previously reported [15, 18]. One patient was headache-free, whereas the majority described severe continuous daily headache pain associated with poor quality of life. Overall headache in patients with active IIH was of moderate pain severity, long daily duration and a mean frequency of 22 days per month, with the associated headache impacting on the individual's quality of life. These observations are in keeping with broader patients' views that the chronic daily headache of IIH is very disabling [6] and is already known to drive reduction in quality of life in IIH [8].

A previous randomized controlled trial in IIH [15] classified 68% with migraine or probable migraine and 26% tension-type or probable tension-type headaches. In the present study 90% reported migraine-like headaches and 70% would fulfil the criteria for a diagnosis of chronic migraine. Furthermore, 40% of participants in the present study described aura. In our cohort tension-type headaches were not common, with only one patient fulfilling the IHS criteria [9]. This may reflect differences between the types of patients recruited to the two trials, for example the IIHTT [15] participants were newly diagnosed patients, whereas the IIH:WT participants reflected a more chronic disease duration (Table 1).

68% of participants reported a prior diagnosis of migraine before being diagnosed with IIH, of whom over half (53%) had been diagnosed with migraine prior to the age of 18 years old and only 11% developed migraine-like headaches following the diagnosis of IIH. This portion of patients with a prior migraine history is considerably higher than that of the general population, where for example one study found the lifetime

Table 3 Predicting changes in headache severity and monthly headache days from changes in intracranial pressure

Time (months)	Change in intracranial pressure (cmH_20)	Change in mean headache severity (95% confidence interval)	Change in mean MHD (95% confidence interval)
12	−5	−0.95 (−2.61, 0.68)	−3.06 (−9.61, 2.91)
12	−10	−1.35 (−2.70, 0.10)	−4.08 (−9.56, 2.80)
24	−5	0.43 (−1.18, 1.96)	− 5.32 (− 11.5, 1.35)
24	−10	− 0.19 (− 1.94, 1.61)	−6.17 (− 13.3, 0.79)

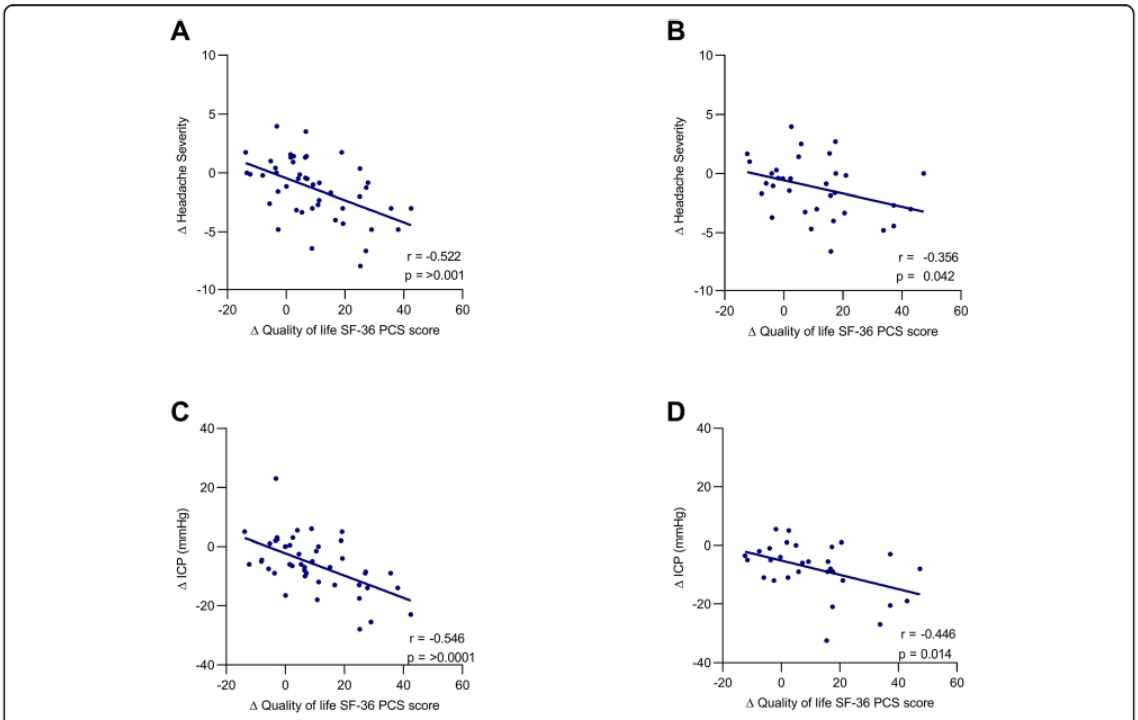

Fig. 3 Correlation of change in Quality of Life SF-36 physical component score (PCS) score and change in headache severity (HS) between baseline and 12 months (**A**) baseline and 24 months (**B**); Intracranial Pressure (ICP) between baseline and 12 months (**C**) between baseline and 24 months (**D**)

prevalence of migraine to be 29% [19]. A number of interesting observations could be postulated, for example, those with a recent diagnosis of migraine could have been initially diagnosed as migraine instead of IIH, however the portion of those with a very longstanding history of migraine are unlikely to have been misdiagnosed. Given the longevity of migraine in our cohort, some patients may have had chronic migraine before diagnosis of IIH, whereas others may have developed chronic migraine-like headaches following diagnosis. It remains unclear whether diagnosis of IIH in patients with known episodic migraine contributes towards transition to chronic migraine and if this is dependent on central sensitization.

Cutaneous allodynia is reported in over half of all patients with migraine [20]. It has not typically been a feature of conditions associated with raised ICP (e.g. brain tumours or hydrocephalus). A previous study reported allodynia in 50% of IIH patients who mostly had a migraine-like headache profile [18]. In the present study 92% reported cutaneous allodynia at the maximum headache severity and although this was not associated with headache severity or frequency at baseline, change in allodynia over 12 months was associated with change in ICP.

Headache management is an unmet need in this disease, with no randomised controlled trials to guide treatment options. Only 18 participants were on concurrent headache preventative therapies, whereas 40 fulfilled the criteria for chronic migraine-like headaches, leaving a large portion of patients under treated. Recently the first prospective open label study of a CGRP monoclonal receptor antibody reported substantial improvements at 3 months, which continued for up to 12 months in the reduction of monthly moderate/severe headache days [13]. This benefit was seen both in those with and without prior migraine and in those with or without prior existing medication overuse headache [13]. Topiramate, a well-known migraine preventative therapy has been evaluated in IIH in the context of the impact on vision, rather than its beneficial effects of reduction of headache disability and is used off label in routine clinical practice [21]. However consensus guidelines for IIH placed topiramate as a useful medication for management of headaches in IIH in order to avoid medicines such as beta-blockers and tricyclics that may exacerbate weight gain, a known precipitant of the disease [1].

Similar to a previous study approximately a third of participants met the diagnostic criteria for medication-

overuse headache at baseline [9]. Medication-overuse headache is particularly common in patients with a background of chronic migraine, for example in the United States it has been reported in up to a quarter. However, there are many factors that influence medication-overuse headache [22, 23]. Advising patients about appropriate usage of headache analgesics and avoidance of opiates is therefore an important part of headache management in IIH [1].

The data presented indicates a relationship between increased ICP and increased presence of migraine-type headache. Change in ICP can predict change in headache over time. In a previous randomized controlled trial of those with recent onset IIH (within 2 weeks of presentation) no correlation between headache characteristics and ICP was found over a 6 month follow-up [15]. Future studies are required to investigate this complex relationship from the acutely presenting patient to the more chronic phase of IIH headache. ICP monitoring studies may further delineate this complex relationship further. Therapies that have been shown to reduce ICP in animal models, such as GLP-1 [24], could be helpful in both reducing headache burden in conditions of raised ICP and weight management in IIH [25].

Conclusions

This detailed prospective evaluation of headache in patients with IIH demonstrates a consistent relationship between headache (severity and monthly headache days) and ICP. Modelling of this relationship between headache and ICP enabled prediction of headache outcomes depending on changes in ICP over a 12 and 24 month horizon. The headache in patients with active IIH is migraine-like in the majority. IIH patients demonstrated markers of allodynia which improved with reduction in ICP. Quality of life measures improved with reduction in ICP and headache. Therapeutic strategies to improve ICP are likely to improve headache in IIH.

Abbreviations

ASC-12: Allodynia Symptom Checklist-12; CGRP: Calcitonin gene-related peptide; CSF: Cerebrospinal fluid; HS: Headache severity; ICP: Intracranial pressure; IIH: Idiopathic intracranial hypertension; IIH:WT: IIH weight trial; IHS: International Headache Society; LP: Lumbar puncture; MHD: Monthly headache days; NRS: Numerical rating system; OP: Opening pressure; PCS: Physical component score

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-021-01321-8.

Additional file 1: Supplemental methods - allodynia checklist.

Additional file 2: Supplemental Table 1- Headache characteristics at baseline.

Additional file 3: Supplemental Table 2 – Pressure allodynia at baseline and 12 months.

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No additional acknowledgements.

Authors' contributions

SM – drafting manuscript, data collection and analysis; BW - drafting manuscript and analysis; ZA, data collection and analysis; JM, data collection and analysis; RO, data collection and analysis; AY, data collection and analysis; MT, data collection and analysis; AG, data collection and analysis; OG, data collection and analysis; GL, data analysis and editing manuscript; AS, editing manuscript, study lead. The author(s) read and approved the final manuscript.

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Availability of data and materials

Data will be made for reasonable requests.

Declarations

Ethics approval and consent to participate

The trial was approved by The National Research Ethics Committee West Midlands – The Black Country, on 28 February 2014 (14/WM/0011). All participants gave written consent after receiving detailed written information. The trial was registered, clinicaltrials.gov identifier: NCT02124486.

Consent for publication

All co-authors consent for publication.

Competing interests

SM - Royalties - Springer publishing: Neuro-Ophthalmology, Global Trends in Diagnosis, Treatment and Management; Consultancy - Invex therapeutics, Neurodiem, Honoraria - Novartis, Santen, Santhera, Allergan, Chuagi, Chiesi; Data safety/advisory boards - Roche, Janssen, Invex therapeutics. BW - Consultancy, Invex Therapeutics; Director Ceftronics Limited; Patent pending, Uk - 1907237.0. ZA – none. JM – none. RO – none. AY - fees for educational talk – TEVA. MT – none. AG – none. OG – none. GL – none. KB - Consultancy, Invex Therapeutics; stock - Astrazenica, GlaxoSmithKline. AS - Honoraria - Chiesi; Safet board/advisory - Novartis; Director / Share options - Invex therapeutics.

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Publisher's Note

Supplemental methods - allodynia checklist:

Allodynia symptom checklist-12

The allodynia symptom checklist response scales are coded as follows:

- Combing your hair: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Pulling your hair back: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Shaving your face: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Wearing eyeglasses: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Wearing contact lenses: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Wearing earrings: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Wearing necklace: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Wearing tight clothing: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Taking a shower: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Resting your face or head on a pillow: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Exposure to heat: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2
- Exposure to cold: Does not apply=0, Never=0, Rarely=0, Less than half the time=1, Half the time or more=2

The total score is calculated by summing the values for each question.

The score ranges from 0 to 24 where a low score is good

The allodynia scores can also be characterised using cut-off values as follows:

0-2 = no allodynia; 3-5 = mild allodynia; 6-8 = moderate allodynia
9 or more = severe allodynia

Supplemental Table 1- Headache characteristics at baseline

Headache location (not mutually exclusive), % (number)	
Bilateral	76% (37/49)
Unilateral Right	20% (10/49)
Unilateral Left	18% (9/49)
Frontal	72% (31/43)
Temporal	47% (20/43)
Parietal	37% (16/43)
Occipital	44% (19/43)
Periorbital	8% (3/38)
Retroorbital	18% (7/38)
Headache quality (not mutually exclusive), % (number)	
Throbbing	73% (32/44)
Pressure	55% (24/44)
Stabbing/Sharp	11% (5/44)
Shooting	7% (3/44)
Unclear	35% (17/58)
Combination of features	45% (20/44)
Associated symptoms, % (number)	
Photophobia	81% (38/47)
Phonophobia	60% (27/45)
Osmophobia	19% (3/16)
Nausea	70% (32/46)
Vomiting	18% (8/45)
Dizzy symptoms	33% (10/30)

	Autonomic features	5% (1/19)
	Pulsatile tinnitus	74% (49/66)
Activity that exacerbated headache		
	Physical activity	53% (19/36)
	Lying flat	32% (9/28)
	Bending	31% (11/35)
	Valsalva manoeuvre	23% (8/35)

Supplemental Table 2 – Pressure allodynia at baseline and 12 months

	Baseline			12 months		
	n	mean	sd	n	mean	sd
F1	54	0.54	1.00	45	0.34	0.77
F2	54	2.10	2.53	45	1.52	2.60
F3	54	7.42	8.49	45	7.69	11.47
HS (0-10)	59	5.02	2.00	49	3.66	2.88
MHD / days	59	22.31	7.76	49	15.67	11.48
ICP / cmCSF	62	34.68	5.69	51	28.88	7.84

Key: sd, standard deviation; von Frey hairs (F1, 0.32g; F2, 8.30g; and F3, 24g); HS, headache severity; MHD, monthly headache days; ICP, intracranial pressure.

Publication 8: Visual Field Pointwise Analysis of the Idiopathic Intracranial Hypertension Weight Trial

Manuscript title:
Mollan SP, Bodoza S, Ní Mhéalóid Á, Mitchell JL, Miller NR, Montesano G, Crabb DP, Wall M, Brock K, Sinclair AJ. Visual Field Pointwise Analysis of the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT). Transl Vis Sci Technol. 2023;12(5):1.

Involvement:
I helped interpret process the raw data. I interpreted the analysis. I wrote the initial draft of the publication. I revised the publication following the extensive critical external review.

Page number: 36

tvst

Neuro-Ophthalmology

Visual Field Pointwise Analysis of the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT)

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Purpose: This study was designed to determine if point analysis of the Humphrey visual field (HVF) is an effective outcome measure for people with idiopathic intracranial hypertension (IIH) compared with mean deviation (MD).

Methods: Using the IIH Weight Trial data, we performed a pointwise analysis of the numerical retinal sensitivity. We then defined a medically treated cohort as having MDs between −2 dB and −7 dB and calculated the number of points that would have the ability to change by 7 dB.

Results: The HVF 24-2 mean ± SD MD in the worse eye was −3.5 ± 1.1 dB (range, −2.0 to −6.4 dB). Total deviation demonstrated a preference for the peripheral and blind spot locations to be affected. Points between 0 dB and −10 dB demonstrated negligible ability to improve, compared with those between −10 dB and −25 dB. For the evaluation of the feasibility for a potential medical intervention trial, only 346 points were available for analysis between −10 dB and −25 dB bilaterally, compared with 4123 points in baseline sensitivities of 0 to −10 dB.

Conclusions: Patients with IIH have mildly affected baseline sensitivities in the visual field based on HVF analyzer findings, and the majority of points do not show substantial change over 24 months in the setting of a randomized clinical trial. Most patients with IIH who are eligible for a medical treatment trial generally have the mildest affected baseline sensitivities. In such patients, pointwise analysis offers no advantage over MD in detection of visual field change.

Introduction

Idiopathic intracranial hypertension (IIH) is characterized by raised intracranial pressure (ICP) associated, in most cases, with papilledema, visual field defects, and, in some cases, permanent visual loss.[1] Most people with IIH have moderate to severe headaches, systemic metabolic dysfunction, and central obesity.[2–4] The incidence of IIH is increasing around the world, commensurate with the increase in worldwide obesity.[5,6] Depending on the severity of IIH, patients can be treated with weight loss alone, ICP-lowering medications such as acetazolamide,

ICP-lowering surgery, or a combination of these. The IIH Weight Trial (IIH:WT) showed that weight loss achieved by bariatric surgery resulted in long-term remission of ICP compared with a lifestyle weight-management intervention.[7]

The Humphrey visual field (HVF) mean deviation (MD) has been used as an endpoint in IIH clinical trials.[8,9] However, although the IIH:WT met its primary endpoint (change in ICP measured by lumbar puncture opening pressure at 12 months), there was no significant improvement seen in the MD in either arm. We thus wondered if a different method—pointwise analysis—might be a more sensitive indicator of a change in the visual field in IIH patients participating in a treatment trial.

There are a number of different ways to evaluate visual field damage.[10–13] The MD determined by the HVF Analyzer (Carl Zeiss Meditec, Dublin, CA) is measured in decibels (dB) using a logarithmic scale and determines the average difference in visual field sensitivity compared with the mean sensitivity of a normal person of the same age. Weighting is inversely proportional to the expected variance at each location in a normal population, effectively giving more weight to the central locations.[14–16] A key regulator, the US Food and Drug Administration, considers a change of 7 dB in MD to be acceptable as being clinically meaningful.[17] In IIH, the expected MD change is smaller compared with other optic neuropathies such as glaucoma. For most patients in an IIH medical intervention trial, a 7-dB change would be unachievable, as the MD inclusion criteria would likely be between −2 dB and −7 dB, which would represent a floor effect.

Another functional endpoint that has been recommended for an optic neuropathy treatment trial is a change of 7 dB in five or more predefined reproducible visual locations.[17] Restricting an analysis to a particular subset of points in the visual field has not been previously prospectively investigated in IIH; however, the IIH Treatment Trial (IIHTT) investigators performed a post hoc pointwise analysis of the HVF. For each of the 52 points, a linear regression analysis was performed with the decibel measurement as the outcome variable and time as the independent variable. The IIHTT investigators demonstrated that peripheral points were more affected than central points. Although the magnitude of change in points was modest, there was significantly more improvement in the acetazolamide treatment arm.[10] Given the lack of correlation in the IIH:WT outcome measures and MD, we hypothesized that a pointwise analysis of the IIH:WT visual field data could potentially reveal localized improvements not demonstrated by the MD. The number of participants required and the number of points that could be predicted to change in an IIH trial population could be determined. The purpose of this study was to assess if point analysis of the HVF would be feasible in a cohort of people with active IIH in the setting of a randomized clinical trial.

Materials and Methods

IIH:WT was a prospective, multi-center, open-label, parallel-group, controlled trial in which participants with IIH were randomized in a 1:1 ratio to a bariatric surgery pathway or the Weight Watchers program, a community weight management intervention (CWI). The study was approved by the Ethics Review Board of the National Research Ethics Committee West Midlands, and the Black Country approved IIH:WT (14/WM/0011). In accordance with the Declaration of Helsinki, all subjects gave written informed consent to participate in the study, and the detailed clinical trial methodology has been published.[18] Anonymized individual participant data will be made available along with the trial protocol and statistical analysis plan. Proposals should be made to the corresponding author and will be reviewed by the Birmingham Clinical Trials Unit Data Sharing Committee in discussion with the chief investigator. A formal data sharing agreement may be required after release of the data has been approved and before the data can be released.

Subjects

Women (18–55 years old) with a body mass index (BMI) > 35 kg/m2 were eligible if they had a clinical diagnosis of active IIH according to criteria outlined by Friedman et al.[19] All participants were recruited between March 2014 and October 2017. Evaluations were performed at baseline, 12 months, and 24 months.[18] The primary outcome was ICP as measured by lumbar puncture; secondary outcomes have been reported elsewhere.[7,18] At each visit, HVF with a 24-2 Swedish interactive threshold algorithm standard test pattern using a size III white stimulus was performed. HVFs were included for analysis if they were considered reliable as defined by less than 15% false-positive rates and 30% fixation losses and false-negative rates according to previous criteria.[20]

Acquisition of Data From the Visual Fields

In this analysis, the raw values of the patient's retinal sensitivity at each of the HVF 24-2 predetermined

points were extracted from pdf scans of the HVFs using a custom data extraction tool based on the Python[21] package "hvf extraction script."[22] This script used Google's tesseract optical character recognition[23] to distinguish text inside a digital image and return the relevant text in a useable format. Although the "hvf extraction script" was not originally intended for use on scanned documents, cleaning the images before processing gave values for the majority of the visual field locations. A manual validation of the total cohort point retinal sensitivity eliminated missing data and discrepancies between the original values and the data extraction tool.

HVF Analysis

To detect pointwise change over the course of the study, the points were categorized by individual pointwise retinal sensitivity at baseline. The mean change in sensitivity was plotted at each point from baseline to 12 and 24 months. Subsequently, the cohort was restricted to a population defined by a baseline MD between −2 dB and −7 dB to simulate a medically managed population. Finally, the number of points in the visual field in the whole cohort and in the restricted simulated medically treated cohort that would be expected to change per sensitivity category were calculated.

Statistical Analysis

Analysis of clinical data was based on the full dataset according to the statistical analysis plan.[7] In this evaluation, analyses were based on a per-protocol analysis. Statistical analysis was performed using R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Data were reported with mean and SD for normally distributed variables and median and range for data that were not normally distributed. Missing clinical data, due to any absence or choice, were excluded from the analysis.

Results

Characteristics of the study population are summarized in Table 1. Retinal sensitivity values for the whole cohort at baseline showed that the central points were less affected than the peripheral points (Fig. 1A). The whole cohort was then categorized according to the extent of their reduced visual function at baseline as per MD category (Figs. 1B–1D). As the visual function declined, the distribution of the average deviation points became increasing prominent in the periphery and around the blind spot.

Table 1. IIH:WT Baseline Characteristics

Characteristic	Total ($N = 66$)
Age at baseline (y), mean ± SD	32 ± 7.8
Duration of IIH diagnosis (y), median (IQR)	1.1 (0.5–2.6)
Number on acetazolamide (%)	19 (29)
Opening lumbar puncture pressure (cm CSF), mean ± SD	35.5 ± 7.0
Weight (kg), mean ± SD	118.5 ± 21.1
BMI, mean ± SD	43.9 ± 7.0
Perimetric MD worse eye (dB), mean ± SD	−3.6 ± 3.7 ($n = 65$)[a]
Frisén grade, worse eye, mean ± SD	2.1 ± 1.0

IQR, interquartile range; CSF, cerebrospinal fluid; BMI, body mass index.

[a]Missing data are indicated in parentheses.

Pointwise Location Sensitivity for Whole Cohort at 12 and 24 Months

Points with baseline sensitivities between 0 dB and −10 dB showed small changes over time points (0–5 dB, mean 0.02 ± 3.1; −5 to −10 dB, mean 2.4 ± 4.7 at 12 months) (Fig. 2, Table 2). Points with sensitivities worse than −10 dB demonstrated a larger improvement over time; for example, at 12 months, between −10 dB and −15 dB, the mean ± SD was 5.78 ± 6.10 dB, and from −15 to −20 dB, the mean was 11.10 ± 5.02 dB (Fig. 2, Table 2). For points with baseline sensitivities of −35 to −30 dB, there was a large SD (mean, 16.51 ± 13.75 dB) (Fig. 2, Table 2) at 12 months. When points with baseline sensitivity between −10 dB and −25 dB were analyzed for the whole cohort, the mean change at 12 months was 8.53 ± 6.75 dB, increasing further to 9.61 ± 6.99 dB by 24 months (Tables 2, 3).

Analysis of Pointwise Sensitivities in the Simulated Medically Managed Cohort

Those with a MD between −2 dB and −7 dB at baseline had a similar distribution of changes in the point-sensitive deviation at baseline (Fig. 2B). Overall, the vast majority of data points that were included were in the 0 to −10 dB category ($n = 4123$), compared with points between −10 dB and −25 dB ($n = 346$) and those between −25 dB and −5 dB ($n = 487$) (Table 4).

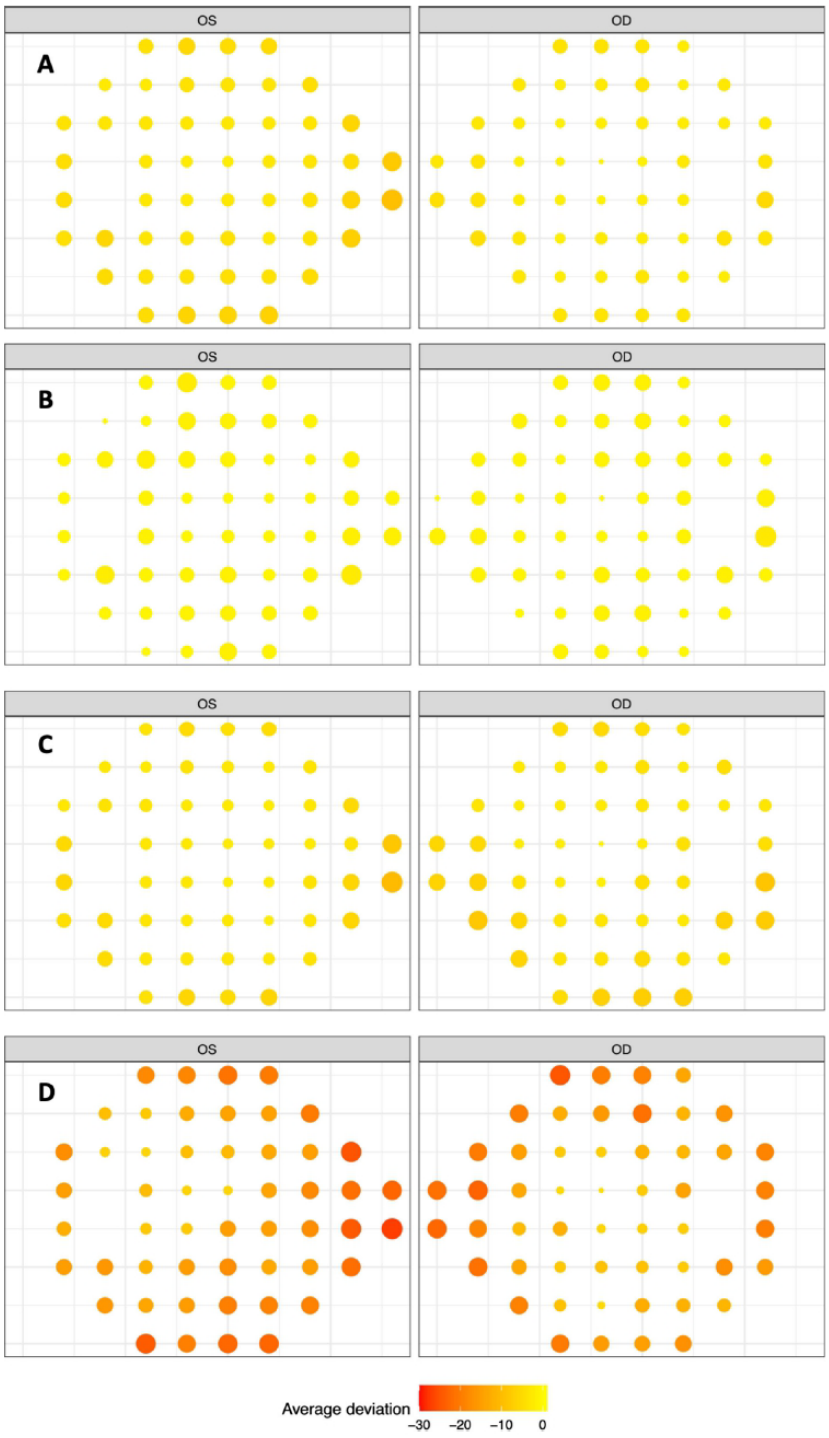

Figure 1. **(A)** The retinal sensitivity at baseline for each location of the HVF for the whole cohort, within eye. All patients were used. **(B)** The retinal sensitivity at baseline for each location of the visual field for those with MDs of −2 dB or better. **(C)** The retinal sensitivity at baseline for each location of the visual field for those with MDs between −2 dB and −7 dB. **(D)** The retinal sensitivity at baseline for each location of the visual field for those with MDs worse than −7 dB.

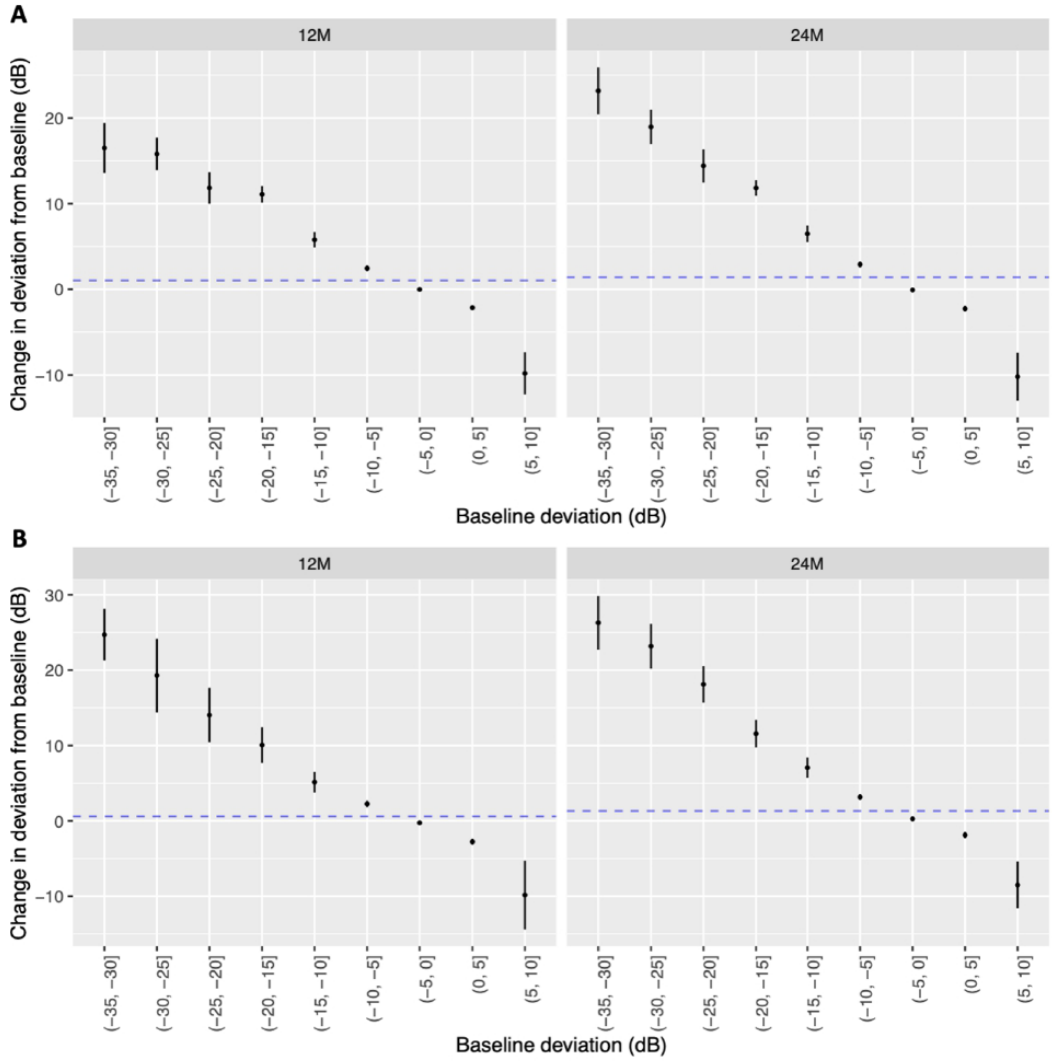

Figure 2. **(A)** The mean change in deviation from baseline (and 95% confidence intervals) to 12 months and 24 months in subsets of points classified by baseline deviation. All patient eyes were used. Categories with at least 10 observations at each time point are shown. The sizes of the groups are naturally different, and this is reflected in the widths of the confidence intervals. **(B)** The mean change in deviation from baseline (and 95% confidence intervals) to 12 months and 24 months in the population defined by MDs between −2 dB and −7 dB at baseline (simulation of a medically treated population).

Analysis of Pointwise Sensitivities in the Whole Cohort

The utility of baseline points between −0 dB and −10 dB was examined to establish how point-sensitivity analysis performed in IIH:WT. As expected, these demonstrated very little change at 12 and 24 months (at 12 months, the mean change was 0.4 ± 3.5 dB; at 24 months, the mean change was 0.48 ± 4.11 dB). Baseline sensitivities between −10 dB and −25 dB have the ability to change over time (Fig. 2). It was only when using the whole cohort that the largest mean changes were found: 8.53 ± 6.75 dB at 12 months and 9.60 ± 6.99 dB at 24 months (Table 3). However, there were fewer points available for analysis (n = 346 at 12 months and n = 329 at 24 months) compared with cases where the baseline pointwise sensitivity ranged from 0 to −10 dB (n = 4123 at 12 months and n = 1844 at 24 months) (Table 4). Furthermore, there was little difference observed between trial arms when analyzing the points that were between −10 dB and −25 dB at baseline, as the bariatric surgery arm was

Table 2. Number of Points and Mean Change in Point Sensitivity in Visual Field Test Locations Categorized by the Baseline Point Sensitivity Subgroup at 12 and 24 Months

Time (mo)	Baseline Point Sensitivity Subgroup (dB)	Number of Points	Mean at Baseline (dB)	Mean Change From Baseline	SD
12	(−35, −30)	85	−32.2	16.5	13.7
	(−30, −25)	56	−26.8	15.8	7.2
	(−25, −20)	67	−21.9	11.8	7.7
	(−20, −15)	103	−17.0	11.1	5.0
	(−15, −10)	176	−11.7	5.8	6.1
	(−10, −5)	711	−6.4	2.4	4.7
	(−5, 0)	3412	−1.7	−0.0	3.0
	(0, 5)	661	1.6	−2.2	3.1
	(5, 10)	11	7.5	−9.8	4.2
24	(−35, −30)	63	−32.0	23.2	11.1
	(−30, −25)	53	−26.8	19.0	7.5
	(−25, −20)	61	−21.9	14.4	7.7
	(−20, −15)	102	−17.0	118	4.6
	(−15, −10)	166	−11.7	6.5	6.4
	(−10, −5)	652	−6.4	2.9	4.5
	(−5, 0)	2784	−1.7	−0.1	3.8
	(0, 5)	480	1.7	−2.3	3.7
	(5, 10)	10	7.4	−10.2	4.5

Table 3. Number of Points and Mean Change in Point Sensitivity Over Time in Test Locations With a Baseline Point Sensitivity Between −10 dB and −25 dB, Categorized by Trial Arm and Use of Acetazolamide

Time (mo)	Group	Number of Points Between −10 dB and −25 dB	Mean	SD
12	Whole cohort	346	85	68
	CWI	127	82	72
	CWI with acetazolamide	22	88	43
	CWI with no acetazolamide	105	80	76
	Bariatric surgery	219	88	65
24	Whole cohort	329	96	70
	CWI	118	115	71
	CWI with acetazolamide	15	70	45
	CWI with no acetazolamide	103	122	72
	Bariatric surgery	211	86	67

Table 4. Subanalysis (Defined by MD Between −2 dB and −7 dB at Baseline) to Simulate a Medically Treated Cohort Where the Number of Point Sensitivities Are Categorized by the Location Point Sensitivity

Baseline Point Sensitivity Subgroup (dB)	Time Point (mo)	Number of Points That Could Be Analyzed	Mean (dB)	SD
0 to −10	12	4123	0.4	3.5
0 to −10	24	3436	0.5	4.1
−10 to −25	12	346	8.5	6.8
−10 to −25	24	329	9.6	7.0
−25 to −35	12	487	10.8	9.1
−25 to −35	24	445	12.6	9.3

8.75 ± 6.51 dB at 12 months and the CWI group was 8.16 ± 7.15 dB at 12 months. This was despite a significant difference between baseline and 12 months in the ICP of −6.0 cm cerebrospinal fluid (CSF) between the trial arms. Among those in the CWI arm who were not on acetazolamide, the point sensitivity mean change between baseline and 12 months was 8.03 ± 7.26 dB. Despite the significant reduction in

Table 5. Longitudinal Mean Pointwise Location Sensitivity Changes in Those With Point Sensitivities Between −10 dB and −25 dB, Categorized by Treatment at 12 and 24 Months

	Total Cohort		Bariatric Surgery		All CWI		CWI and No Concurrent Acetazolamide Treatment		CWI and Concurrent Use of Acetazolamide	
	Mean ± SD (*n*)	Effect Size	Mean ± SD (*n*)	Effect Size	Mean ± SD (*n*)	Effect Size	Mean ± SD (*n*)	Effect Size	Mean ± SD (*n*)	Effect Size
12 mo	8.53 ± 6.8 (346)	1.27	8.75 ± 6.5 (219)	1.34	8.16 ± 7.2 (127)	1.14	8.77 ± 4.3 (22)	2.04	8.03 ± 7.6 (105)	1.05
24 mo	9.60 ± 6.99 (329)	1.37	8.55 ± 6.7 (211)	1.27	11.5 ± 7.1 (118)	1.62	12.16 ± 7.2 (103)	1.69	7.00 ± 4.52 (15)	1.55

ICP found between the bariatric surgery group and the CWI group, there was little discrimination analyzing point sensitivities among bariatric surgery, CWI, CWI with no acetazolamide treatment, and CWI with concurrent use of acetazolamide (Table 5).

Categorizing the Population by Baseline MD

To understand how representative a baseline point sensitivity beyond −10 dB in one or more points was in an active IIH population, we calculated the number of points ≥ −10 dB in each individual (Table 6). In the whole cohort, the median number of points on the baseline visual field worse than −10 dB was 5 (interquartile range, 2–13), with 57% of the cohort having at least two points worse than −10 dB at baseline (Table 6). In the subgroup with a MD between −2 dB and −7 dB at baseline, 42% had more than five points that were worse than −10 dB. As the number of points required for analysis decreased, more participants were available for inclusion; for example, 73% had at least two or more points, and 85% had one point worse than −10 dB (Table 6). Also, 31% of patients at 12 months and 38% at 24 months would have achieved five or more points that improved by 7 dB (Table 7).

Discussion

In this study, we characterized the pointwise pattern of visual field change in a cohort of people with active IIH recruited to the IIH:WT. Those with baseline point sensitivities between 0 dB and −10 dB showed small changes over time and, as expected, were unlikely to demonstrate clinically meaningful change over both 12 and 24 months. Points in the −10 to −25 dB category demonstrated change that could be considered clinically meaningful (mean of 8.5 dB in at least one point in the whole visual field); however, using data between −10 dB and −25 dB resulted in fewer data points and larger SDs for analysis. Although the median number of points worse than −10 dB was five, 43% of all of the IIH:WT participants had fewer than two points worse than −10 dB at baseline, emphasizing that data points worse than −10 dB were not representative of the majority of IIH patients.

It should be emphasized that eligibility for the IIH:WT was not determined by MD criteria. Therefore, to simulate the HVF data to reflect a typically medically managed cohort, we chose a baseline HVF in which the MD was between −2 dB and −7 dB (the criterion range used in the IIHTT[9]). Among this group,

Table 6. Number of Participants Who Had One or More Baseline Points in Either Eye With a Sensitivity Worse Than −10 dB in the Entire Cohort With and Without Perimetric MD Criteria

		Number of Points ≤ −10 dB in Either Eye at Baseline (%)					
Population	*n*	1	2	3	4	5	Median Points (IQR)[a]
Whole cohort	58	39 (0.67)	33 (0.57)	26 (0.45)	20 (0.35)	20 (0.35)	5 (2–13.5)
MD ≥ −2 dB	38	33 (0.87)	29 (0.76)	22 (0.58)	19 (0.50)	19 (0.50)	6 (2–15)
MD between 2 dB and 7 dB	33	28 (0.85)	24 (0.73)	17 (0.52)	14 (0.42)	14 (0.42)	4 (2–10)
MD ≤ −7 dB	6	6 (1.00)	6 (1.00)	6 (1.00)	6 (1.00)	6 (1.00)	50.5 (32.75–71.25)

[a]The median number of points ≤ −10 dB in either eye at baseline (and IQR) in only those patients who had at least one qualifying point.

Table 7. Percentage and Number of Participants Who Had Pointwise Improvement of 7 dB or More From Baseline at 12 and 24 Months

Number of Available Points on the HVF 24-2 at Baseline	Patients Who Had a Pointwise Improvement of 7 dB or More From Baseline at	
	12 mo (*N* = 53), % (*n*)	24 mo (*N* = 44), % (*n*)
0	26 (14)	18 (8)
1	13 (7)	9 (4)
2	6 (3)	7 (3)
3	4 (2)	7 (3)
4	1 (7)	1 (4)
5	1 (4)	1 (5)
>5	30 (16)	37 (17)

42% had five or more points worse than −10 dB at baseline (Table 7). If only two points were required for analysis, 73% had two or more points worse than −10 dB in either eye at baseline (Table 6). Thus, we found that it would be challenging to use point analysis as an outcome for an interventional medical trial in IIH, as the pool of point-sensitivity data available for meaningful analysis would be extremely small. Additionally, the participants overall would be less representative of the whole disease spectrum, which could affect the applicability of the results being directly translatable to clinical practice. Finally, test locations with 8 to 18 dB of loss at baseline had a 95% prediction interval that nearly covered the full measurement range of the instrument (0–40 dB)[24]; thus, the test–retest variability of these locations was so poor that there was little signal above the variability-related noise.[25]

There is no universally adopted, minimally clinically important change in HVF measures in IIH as there are in glaucoma.[17,26,27] In glaucoma, visual field progression equal to or faster than −0.5 dB per year for at least five abnormal test locations at baseline has been found to be clinically significant,[28] as have changes from baseline beyond the 5% probability levels for the Glaucoma Change Probability analysis in five or more reproducible visual field locations.[29] Although pointwise analysis in patients with IIH has revealed changes around the blind spot and in the nasal area, likely reflecting the reduction in optic head nerve swelling as the papilledema resolves,[10] visual fields with global diffuse damage, such as occur in patients with IIH, tend to be more variable than fields with focal damage such in glaucoma.[30] The fundamental differences between these diseases confound the applicability of glaucoma outcome measures to IIH trials. IIH is a rare condition compared with glaucoma which immediately affects the trial design and recruitment potential, particularly as other tools that assess visual function, such as visual acuity (Snellen or logMAR), color vision, and contrast sensitivity, have not been found to be discriminatory in medically managed IIH.[9,30]

A limitation of this study is that it included only patients with well-established IIH. Thus, the results may not be applicable to patients with recently diagnosed IIH or to severely affected patients who may require urgent surgery.[6,31] In addition, because our cohort was small, it was subject to regression to the mean with respect to the mean deviation (Fig. 2). Regression to the mean is a common statistical phenomenon that occurs when repeated measurements are made on the same subject. Subjects would not be expected to have the same measurements at two different times due to measurement error and random fluctuation. Regression to the mean needs to be considered to distinguish a real change from the expected change due to the natural variation in test readings. To minimize regression to the mean, participants should be randomized to study arms, with a control arm being fundamental to the design of the trial. Variability can be further reduced by selecting participants using two or more baseline measurements, resulting in better estimates of the mean and the within-subject variation.

In this study and in studies reported by others,[10] the visual field deficit in IIH typically occurs across the full VF and increases with eccentricity.[13]

Unfortunately, these are the very points that show the largest variability in visual field testing.[32,33] Visual field tests also have been found to be unreliable when visual field locations have sensitivity below 15 to 19 dB because of a reduction in the asymptotic maximum response probability.[34] In addition to test limitations, there are demonstrable changes in cognition in the domains of attention and executive function that have been found in patients with IIH and that directly affect the performance indicators in HVF testing.[35]

Our data indicate that point analysis of the HVF has no advantage over global MD analysis, at least in the population we studied from the IIH:WT. As expected, baseline points that were better than −10 dB had little room to improve over time and, thus, offered little utility for analysis. If the generic threshold for a clinically meaningful change of 7 dB is recommended for IIH treatment trials, baseline points in the range of −10 to −25 dB would be needed for analysis. The US Food and Drug Administration has stated that visual field loss has likely occurred if ≥5 visual field locations have significant change beyond the 5% probability level or if there is at least a 7-dB between-group mean difference for the entire field.[17] A pointwise approach for people with IIH is not feasible as demonstrated here because there are too few data points available for analysis. Additionally, the points that could be used are known to be more variable. In our study, even when a limited threshold was set to determine a clinically meaningful change, point analysis did not offer an advantage over global MD. Consequently, point sensitivity analysis in medically treated IIH is likely to be prohibitive in clinical trials and not representative of the IIH disease spectrum. In addition, if the requirement of regulators for a meaningful change in MD is a 7-dB difference between trial arms, as recommended for glaucoma treatment trials,[17] then using MD as a primary outcome would not be achievable in medical IIH trials, as these typically recruit participants with MDs between −2 dB and −7 dB. Future studies may consider investigating the use of a larger stimulus size that has been demonstrated to retain the ability to detect defects, lower retest variability, and improve the useful dynamic range of the instrument.[36,37]

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Publication 9: Guidelines of the International Headache Society for Controlled Clinical Trials in Idiopathic Intracranial Hypertension

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Guidelines

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Abstract

The quality of clinical trials is essential to advance treatment, inform regulatory decisions and meta-analysis. With the increased incidence of idiopathic intracranial hypertension and the emergence of clinical trials for novel therapies in this condition, the International Headache Society *Guidelines for Controlled Clinical Trials in Idiopathic Intracranial Hypertension* aims to establish guidelines for designing state-of-the-art controlled clinical trials for idiopathic intracranial hypertension.

Keywords

Guidelines, Randomised control trial, Pseudotumor cerebri, papilloedema, raised intracranial pressure, headache, vision, drug, lumbar puncture, Idiopathic intracranial hypertension

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Introduction

Idiopathic intracranial hypertension (IIH) is characterized by raised intracranial pressure (ICP) and papilledema with the potential risk of permanent visual loss (1). The incidence rates of IIH have been correlated with country-specific World Health Organization obesity rates with a pooled incidence of 1.2 per 100,000 people (2). There is a peak incidence in women around the age of 25 years, reported in one study to be 15.2 per 100,000 (3). With increasing rates of obesity globally, there has been marked increase in the incidence of IIH observed around the world (2–4).

Headache is a predominant symptom (5,6). IIH has a detrimental effect on all aspects of the patient's quality of life (QOL) which has been found to be predominately driven by headache (7–9). The current International Classification of Headache Disorders 3rd edition (ICHD-3) classifies headache attributed to IIH as a secondary headache disorder (10).

The 2015 Cochrane review concluded that there is a lack of evidence to guide management of IIH (11), as there are few published randomized clinical trials (RCTs) and only a few open label trials (Table 1 and 2) (12–20). To date, research has been sporadic due to the relative rarity of the disease but with the increasing incidence and prevalence of the disease there is an unmet medical need for effective acceptable interventions. The James Lind Alliance Priority setting Partnership, a National Institute of Health and Care Research supported initiative, was conducted in IIH and funded by IIHUK, a United Kingdom Charity for people living with IIH. This defined uncertainties in diagnosis and management that should be prioritized for research, as determined by patients, caregivers and health care physicians (21).

IIH is a disease that requires a multi-disciplinary approach and that poses challenges for trial design and choice of trial outcomes. IIH teams require a broad group of specialists, including ophthalmologists, neurologists, headache specialists, neurosurgeons, endocrinologists and dieticians (1,22). This also indicates the complexity of the disease management (23,24). The International Headache Society (IHS) has a track record of using an evidence-based approach to define the standards for the conduct and reporting of RCTs in headache disorders (25–31). Guidelines recommend standardized approaches to methodology and to define meaningful outcomes. Trial outcomes need to be sufficiently flexible to address the intervention type – valid by measuring what matters – reliable and clinically meaningful. Defining key trial outcomes is critically important for the ability to meta-analyze data from different trials. Regulatory bodies, such as the United States Food and Drug Administration and The Committee for Medicinal Products for Human Use at the European Medicines Agency, rely on the results of clinical trials to reach opinions as to whether or not to authorize various medicines and devices. These guidelines will therefore cover designs for both pharmacological treatments as well as for non-pharmacological treatments such as weight loss methods and surgery. Patient-reported quality of life and cost-effectiveness are important to support decisions regarding reimbursement. This guideline is designed to advance the quality of future IIH trials and will subsequently help improve finding meaningful treatments for people with IIH. Given that IIH is rarer in prepubertal children, and potentially has a different underlying pathogenesis (32), the present guidelines will primarily focus on those post-puberty and adults. The present guidelines will only address IIH and not secondary pseudotumor cerebri syndrome nor Idiopathic Intracranial Hypertension without Papilledema (IIHWOP) as these are rare conditions with likely alternative underlying pathophysiology (33–35).

Previous trials in IIH

There have been few RCTs in IIH and a small number of cohort studies (Table 1 and 2) (12–20). Choice of the primary outcome has varied between visual field status, as assessed using automated perimetry performed on the Humphrey field analyzer, and ICP as measured by lumbar puncture (Tables 1, 2 and 3). Note that, to date, there has been no RCT evaluating treatment for headache attributed to IIH, although an open-label study recently reported the use of a primary end point of change from baseline in monthly moderate and severe headache days at 12 months (18). Trials evaluating medicines often have different outcomes compared with surgical trials for interventions. A recent study on the design of trials and the common data elements reported in IIH, as identified by clinicaltrials.gov, highlighted the extreme heterogeneity in outcome reporting (36). Trial considerations for IIH require a systematic approach as this is a multispecialty disease where there still is uncertainty regarding treatment approaches depending on the leading specialty and/or disease severity. In recent years, a number of observational cohort studies have been published that are now helping

Table 1. Summary of published randomized controlled trials for the treatment of IIH.

Trial	Design, location	Phase	Interventions	Primary outcome	Secondary outcomes	Length of trial	Disease duration	Participant demographics	Anticipated *versus* actual withdrawal rate	Results
IIH Pressure Mitchell et al. 2022 (12)	Randomized control trial. Single center in United Kingdom	2a	Exenatide, a Glucagon like peptide-1 receptor agonist, (10 mcg twice daily sub-cutaneous) *versus* placebo	Intracranial pressure as measured by telemetric, intraparenchymal intracranial pressure monitor (Raumedic™)	*Headache outcome:* headache impact test (HIT-6) score; monthly headache days. *Visual outcomes:* LogMAR visual acuity; Visual fields (measured on automated Humphrey perimetry); Papilledema, as measure on optical coherence tomography.	12 weeks	All that meet criteria for a diagnosis of IIH.	N = 16 100% Women Mean age [Mean BMI 38.1±6.2 kg/m^2, Mean ICP 30.6 ± 5.1 cmH2O]	16 participants were recruited, 15 completed the study.	ICP was significantly lower at all timepoints: 2.5 hours -5.7 ± 2.9 cmH_2O ($p = 0.048$); 24 hours of -6.3 ± 2.9 cmH_2O ($p = 0.030$); and 12 weeks -5.6 ± 3.0 cmH_2O ($p = 0.058$) Monthly headache days fell in the Exenatide treated cohort (−7.7 (9.2) $p = 0.069$) and vision improved (logMar acuity −0.1 (0.04) $p = 0.004$).
IIH Weight Mollan et al. 2021 (13)	Randomized control trial. Multicenter (5 sites) in United Kingdom	3	Bariatric surgery *versus* a community weight management intervention (CWI) [Weight Watchers™]	Change in intracranial pressure measured by lumbar puncture opening pressure (LP OP) at 12 months	LP OP at 24 months *Headache outcomes:* Headache Impact Test-6 disability questionnaire (HIT-6), severity scores (numeric rating scale 0 to 10 maximum), frequency (days per month), and analgesic use (days per month) *Visual outcomes:* logarithm of the minimum angle of resolution (logMAR) visual acuity (VA); contrast sensitivity assessed by Mars letter contrast sensitivity test (Mars Perceptrix, USA); perimetric mean deviation (PMD) using Humphrey 24-2 Swedish interactive thresholding algorithm (SITA) *Patient reported outcomes:* Health-related quality of life measured by short-form [SF]-36, the Hospital Anxiety and Depression Scale, and EuroQol 5 Dimensions [EQ-5D-5L] questionnaire	12 months, with 24 months and 5 year follow-up	All that meet criteria for a diagnosis of IIH.	N = 66 100% Women Mean age, 32 years	Anticipated :28% dropout rate Actual: 66 women randomized, 64 remained in the trial at 12 months, with 54 (82%) completing the primary outcome.	Intracranial pressure was significantly lower in the bariatric surgery arm at 12 months (adjusted mean difference -6.00cm H_20 95% confidence interval [CI] −9.5 to −2.4]; p = .001) and at 24 months (adjusted mean difference -8.2 cmH_2O [95% CI, −12.2 to −4.2]; p < .001) compared with the CWI arm
IIH Drug trial Markey et al. 2020 (14)	Randomized control trial. Multicenter (3 sites) in United Kingdom	2b	11β-Hydroxysteroid dehydrogenase type 1 inhibitor, AZD4017	Intracranial pressure as measured by lumbar puncture opening pressure [90% power (alpha = .05) to detect a difference of 14% in ICP (assuming a	Safety	12 weeks	All that meet criteria for a diagnosis of IIH.	N = 31 100% Women Mean age 31.2 (SD = 6.9) years	20% allowance for withdrawal	AZD4017 was safe, with no withdrawals related to adverse effects. Exploratory analysis found the AZD4017 mean ICP change:

(continued)

Table 1. Continued

Trial	Design, location	Phase	Interventions	Primary outcome	Secondary outcomes	Length of trial	Disease duration	Participant demographics	Anticipated *versus* actual withdrawal rate	Results
				standard deviation of 10% for ICP)].						-4.3 cmH_2O (SD = 5.7); $P = 0.009$. Note this was an ICP reduction by 12%. Placebo mean ICP change placebo group [mean change: -0.3 cmH_2O (SD = 5.9); $P = 0.8$
SIGHT surgical trial 2020 (15)	Randomized control trial. Multicenter in North America	3	Ventriculoperitoneal Shunt *versus* Acetazolamide *versus* Optic nerve sheath fenestration	Humphrey visual field Perimetric mean deviation	Time of treatment failure of the eligible eye(s), followed by a continuation study to assess time to treatment failure.	26 weeks	..	N = 180	..	Closed due to enrolment targets not achieved.
Wall et al. 2014 (16)	Randomized control trial. Multicenter (38 sites) in North America	3	Acetazolamide plus low-sodium weight-reduction diet *versus* Placebo plus low-sodium weight-reduction diet	Humphrey visual field Perimetric mean deviation (PMD)	*Visual outcomes:* PMD changes in least affected eye; papilledema Frisén grade; visual acuity. *Quality of life:* visual quality of life (VFQ-25), quality of life (36-Item Short Form Health Survey). *Headache outcome:* headache impact test (HIT-6) score. *Other outcomes:* CSF pressure, weight, vital signs, laboratory results.	26 weeks	Acute, no more than 2 weeks of treatment for IIH, and within 1 week if treated with acetazolamide	N = 165 Women = 161 Men = 4 Average age was 29 years (range, 18–52 years).	10% allowance for withdrawal; actual withdrawal rate of 19%.	The mean improvement in PMD was greater with acetazolamide (1.43 dB, from -3.53 dB at baseline to -2.10 dB at month 6; n = 86) than with placebo (0.71 dB, from -3.53 dB to -2.82 dB; n = 79); the difference was 0.71 dB (95% CI, 0 to 1.43 dB; $P = .050$)
Ball et al. 2011 (17)	Open-label, parallel-group randomized control trial. Multicenter (6 sites) in United Kingdom	3	Acetazolamide *versus* placebo	Disease remission as determined by physician	*Symptoms:* Headache (subjective patient-reported 10-point scale); tinnitus (subjective patient-reported presence versus absence); visual obscurations *Visual outcomes:* LogMAR visual acuity; Contrast sensitivity (measured on Pelli-Robson chart); Visual fields (measured on automated Humphrey perimetry); Papilledema; *Other:* Hospital Anxiety and Depression Scale score; patient rated health status (measured on EuroQoL and Short Form 36).	52 weeks	All that meet criteria for a diagnosis of IIH.	N = 50 Women n = 46 Men n = 4 Median age 29 years in acetazolamide group and 33 years in the placebo group.	20% did not complete 12 month follow-up	44% judged to have IIH in remission at the end of the trial. The odds ratio for remission/improving was 0.7 in favor of acetazolamide [95% confidence interval (CI) 0.2–2.9]. The mean final status score was 2.6 in the acetazolamide arm compared with 2.9 in the control arm (difference -0.3, 95% CI -1.6 to 0.9) Difficulties with recruitment were highlighted as well as poor compliance with acetazolamide therapy (12 patients). Based on the study data, a sample size of 320 would be required to demonstrate a 20% treatment effect in a substantive trial

Table 2. Summary of open label therapeutic and lifestyle interventions in idiopathic intracranial hypertension.

Author, Year	Trial design, location	Study intervention	Outcomes	Length of study	Disease state	Participant demographics	Results
Yiangou et al 2020 (18)	Prospective, single center open label study in those with persistent post IIH headache. Birmingham, United Kingdom	Erenumab, a calcitonin gene-related peptide monoclonal antibody	*Primary outcome:* change in monthly moderate/ severe headache days from baseline (30-day pre-treatment period) compared to 12 months. *Secondary outcomes:* HIT-6 score Headache severity Analgesic days Quality of life Short Form-36 Health Survey	12 months	>1 year; IIH in ocular remission and those with post-IIH persistent headache	N = 55; 100% women; Mean (SD) age 35.3(9) years.	Mean (SD) [CI] reduction in monthly moderate to severe headache days was 10.8 (4.0) [9.5, 11.9], $p < 0.001$ and in total monthly headache days reduced by 13.0 (9.5) [10.2, 15.7], $p < 0.001$ Headache impact test-6 score and quality of life Short Form-36 Health Survey significantly improved at 12 months.
Sinclair et al 2010 (19)	Prospective, multi-center cross over cohort study. Birmingham, United Kingdom	Very low energy diet (425 kcal/day)	*Primary outcome:* Intracranial pressure *Headache secondary outcomes:* HIT-6 score Headache frequency Headache severity Analgesic days *Visual secondary outcomes:* Papilledema - ultrasonography of the elevation of the optic disc and diameter of the nerve sheath - optical coherence tomography peripapillary retina nerve fiber layer - Frisén grade Visual function - LogMAR visual acuity - mean deviation of Humphrey visual field. *Other secondary outcomes:* Symptoms	9 months (3 months control phase; 3 months Very low calorie diet; 3 months follow-up.)	Active IIH fulfilling Friedman criteria for diagnosis of IIH.	N = 25 100% women. Mean (SD) age was 34.4 (9.2) years.	Significant reductions in weight (mean 15.7 (SD 8.0) kg, P < 0.001), intracranial pressure (mean 8.0 (SD 4.2) cm H(2)O, P < 0.001), score on headache impact test (7.6 (SD 10.1), P = 0.004), and papilledema (optic disc elevation (mean 0.15 (SD 0.23) mm, P = 0.002), diameter of the nerve sheath (mean 0.7 (SD 0.8) mm, P = 0.004), and thickness of the peripapillary retina (mean 25.7 (SD 36.1) micro, P = 0.001))
Celebisoy et al. 2007 (20)	Prospective, single center open label study. Turkey.	Topiramate *versus* acetazolamide	*Primary outcome:* Bespoke visual field grade *Secondary outcomes:* Symptoms Snellen visual acuity Papilledema Frisén grade	12 months	Active IIH fulfilling Friedman criteria for diagnosis of IIH	N = 40 Women n = 35; Men n = 5. Median age of onset in the acetazolamide group was 35 years, and 32 years in the topiramate group.	Visual field grade improved at. all time points of 3, 6 and 12 months as compared to baseline in both groups ($p < 0.0167$). No statistically significant difference between the two groups in visual field grade was present. Prominent weight loss was recorded in the topiramate group.

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Table 3. Potential primary outcome measures for trials evaluating people with IIH.

Target		Outcome Measure
Underlying pathophysiology	Intracranial pressure	Lumbar puncture opening pressure (cm or mm CSF) measured in left lateral decubitus position
		Intracranial pressure by telemetric device (mmHg)
	Weight measures	Body Mass Index
		% weight change
Headache symptoms	Headache	Monthly headache days
		Moderate to severe monthly headache days
		Headache responder rate ($\geq$50% reduction)
		Headache responder rate ($\geq$30% reduction)
		Headache Freedom ($<$ 1 day each month)
		Monthly days with analgesic or migraine specific drugs
		Headache severity (numerical rating scale)
		Most bothersome symptom
Signs	Visual function	Visual acuity
		Contrast sensitivity
		Color vision
		Pupillometry
		Perimetric mean deviation
		Electrodiagnostic testing parameters
	Papilledema	OCT global peripapillary Retinal Nerve Fiber Layer (RNFL)
		OCT total retinal thickness measured from the RNFL scan
		OCT optic nerve head volume measures
		OCT Bruch's membrane opening
		Frisén classification grade
	Ganglion cell loss	OCT macular ganglion cell layer volume or ganglion cell layer and inner plexiform analysis thickness.

to unravel the full disease spectrum, allowing more clarity on the sub-groups of IIH that may benefit from a particular intervention (37–40).

1.1. Selection of subjects

1.1.1. Idiopathic intracranial hypertension definition.
Recommendations:

a. Eligible subjects should fulfil the internationally accepted diagnostic criteria for IIH (41).
b. For trials in which the primary outcome is headache, eligible patients should fulfil the diagnostic criteria for headache attributed to IIH according to the most recent version of the International Classification of Headache Disorders (ICHD) of the International Headache Society (IHS).

Comments:

a. As papilledema is a key criterion for a definite diagnosis of IIH best practice would ensure that pseudopapilledema is excluded (1).
b. As lumbar puncture opening pressure is a key criterion for a definite diagnosis of IIH, best practice would ensure that the left lateral decubitus position of the patient in the lumbar puncture procedure when the opening was recorded should be documented.
c. There are a number of confounding factors in measuring lumbar puncture opening pressure accurately (41–43). For example, Valsalva maneuver (43), a curled body position and the use of sedation can increase ICP measurements. Whereas hyperventilation or repeated attempts may decrease the opening pressure artificially. Any controllable factors should be minimized where possible (1,22,41).
d. Clinical trials for IIH should include all adults who meet these criteria, regardless of ethnicity or sex, to avoid population bias.
e. Diagnostic criteria evolve with the advent of newer technologies and by prospective validation. Magnetic resonance imaging (MRI) by bespoke clinical protocols for raised ICP (44) or routine clinical protocols (45,46) have been evaluated and MRI findings have found to be predictive of raised ICP.
   - Mallery et al. (45) found in a retrospective cohort that three of four MRI features of raised ICP distinguished between patients with IIH and controls with a moderate degree of sensitivity (64%) and high specificity (97%). Reduced pituitary gland height (PGH)

was the most sensitive individual feature (80%) but had low specificity (64%); increased mean optic nerve sheath diameter (ONSD) was less sensitive (51%) and only moderately specific (83%) for identifying IIH without papilledema (IIH WOP). Flattening of the posterior globe (FPG) had low sensitivity (57%) but was the most specific individual feature (90%–99% specific). Venous imaging in this study was only performed in people with IIH and transverse sinus stenosis (TSS) was of moderate sensitivity (78%).

- Hoffmann et al. (44) found PGH to have a sensitivity of 88% and 76% specificity; ONSD with a sensitivity of 80% (left eye) and 72% (right eye), and 96% specific in either eye. FPG had a low sensitivity at 28% but was highly specific at 100%. TSS had a sensitivity of 36% and a specificity of 96%.
- Korsbaek et al. (46) in a prospective cohort found that three of four MRI features were found to distinguish between patients with IIH and non-IIH with a moderate degree of sensitivity (59.5%) and highly specific (93.5%).

1.1.2. Duration of disease.
Recommendation:

The definition for the duration of disease should be clearly stated in the trial inclusion criteria. The history may be based on subject recall, medical records, or both.

Comment:

a. At present, there is no consensus for defining duration of the disease. For example, onset of IIH could be defined as soon as the diagnosis is suspected from the history or as soon as the patient is found to have papilledema (Table 4).

1.1.3. Disease state.
Recommendation:

a. The definition for the disease state should be clearly stated in the trial inclusion criteria. This should be based on history and examination from the medical records.

Comment:

a. At present, there is no consensus typology on the definitions for disease states (Table 4).

1.1.4. Age at entry to adult studies.
Recommendation:

a. Adult subjects participating in clinical trials should be between >18 years and <60 years of age at entry.

Comments:

a. The age at which minors are able to provide informed consent for enrolment in research studies differs around the world. For example, The Medicines for Human Use Regulations prohibit children under the age of 16 years from giving consent to take part in a Clinical Trial of an Investigational Medicinal Product (CTIMP). However, both in Europe and in the United States regulations and law have set the age of 18 years for informed consent for research studies.
b. Few adults will be excluded by the upper limit of this criterion, as IIH beginning after the age of 60 years is extremely rare and secondary pseudotumor cerebri syndrome is more likely to be diagnosed after this age (2–4).

Table 4. Definitions of disease state.

Category	Definition
At onset	The diagnosis of IIH is confirmed and preferably before treatment is initiated.This could also be defined as soon as the diagnosis is suspected from the history or as soon as the patient is found to have papilledema or at the time of diagnostic lumbar puncture.
Fulminant IIH	The diagnosis of IIH is confirmed and there is presence of active severe papilledema with evidence of visual loss or those with documented rapidly declining visual function both of which require surgical intervention to prevent further visual loss.This can occur at any stage of disease.
IIH in ocular remission	The diagnosis of IIH has been confirmed and in whom the papilledema has resolved.
Persistent post-IIH headache	The diagnosis of IIH has been confirmed and there is currently no papilledema, but ongoing headaches.
IIH in clinical remission	The diagnosis of IIH has been confirmed and there is currently no papilledema, and the headaches have resolved.
IIH relapse	The diagnosis of IIH has been previously been confirmed and gone into remission; however relapse is evidenced by return of papilledema or documented return of raised ICP.

1.1.5. Entry to trials involving adolescents.
Recommendations:

a. Adolescent subjects participating in IIH clinical trials should be recruited following onset of puberty.
b. The Tanner staging could be used to define puberty (47,48).
c. Children (those who are yet to undergo puberty) should not be included in adolescent trials.

Comments:

a. There are a number of different assessments that can be used to determine pubertal status (49).
b. The second highest incidence of IIH is found in females over the age of 13 years. This was demonstrated in one study where incidence in women was highest in the 20- to 29-year age group (16.5 per 100 000 person-years) followed by the 13- to 19-year age group (8.7 per 100 000 person-years) and the 30- to 39-year age group (8.4 per 100 000 person-years) (3).
c. IIH following onset of puberty has the same phenotype as the adult condition (32,50) Available treatment options are limited as there has been no prior RCT that has enrolled adolescents. It is therefore important to offer these patients access to novel treatment strategies but also to allow for adapted clinical trial rules, as for orphan diseases.
d. Of note, in the European Union extrapolation of data from adult trials can be used as evidence for licensing of medicines in adolescents (51).

1.1.6. Sex.
Recommendations:

a. Both females and males with IIH should be eligible to participate in IIH clinical trials.
b. The trial design should account for the differences in prevalence of IIH between females and males. This could include stratification by sex or using sex as an interaction term within in the statistical analysis models.
c. Whenever possible, a pre-specified sub-analysis could be considered to evaluate a possible sex difference in response.

Comments:

a. Sex should be recorded for clinical trial purposes, as the sex recorded at birth. This is important for sub-analysis where it is known that males have worse visual outcomes as compared to females (52).
b. IIH is much more prevalent in women than in men, on the order of approximately 10 females to 1 male (2,3).
c. Enrolling males requires caution for the exclusion of secondary causes (34).
d. Special caution should be taken to avoid enrolling women who may be pregnant or breast feeding, unless they are the target of the trial.
e. All fertile-age participants should practice effective contraception.
f. Partners of fertile-age female participants should practice effective contraception.
g. Those who may be transitioning between genders, and are undergoing hormonal therapies, such a testosterone replacement, who are subsequently diagnosed with raised ICP may be regarded as having secondary pseudotumor (53), and therefore not admissible to IIH trials.

1.1.7. Concomitant drug use.
Recommendations:

a. The trial protocol should prespecify concomitant medications that are permitted at enrolment or during the trial and those that are not.
b. Medicines that may influence the trial outcome should be stopped prior to the trial baseline visit with a wash out duration depending on the type of molecule.

Comments:

a. The mechanisms of absorption, distribution, elimination and metabolism of small molecule drugs differ significantly from biological agents.
b. If the trial drug has a specific action that would confound the validity of the outcomes, such as ICP lowering, then any medicines that alter CSF dynamics (such as ICP lowering drugs, or other examples such as retinoids and indomethacin) must be carefully considered as to their acceptability for concomitant use.
c. Concomitant medication use should be considered in the statistical analysis plan a priori and where applicable the analysis of participant data, when there is use of concomitant medication that lowers ICP, should be clearly described in the estimand intercurrent framework in the section describing intercurrent events.
d. Any medicines that would not be acceptable for concomitant use should have a recommended wash out period of at least five and a half drug half-lives.
e. An alternate option would be if concomitant medications are permitted, depending on their action, they could be stratified for at randomization. Specific medicines that could be stratified for include diuretics, glucocorticoids or other ICP lowering agents including topiramate depending on disease stages as indicated above (see section 1.2.4 Stratification).

f. Depending on the investigational medicine product some concomitant medications such as simple analgesics should be recorded in order to avoid MOH but may need no stratification.

1.1.8. Comorbidities.

Recommendations:

a. Patients with severely disabling concomitant disorders that may influence the conduct of a trial or the interpretation of its results, or that would be negatively impacted by the new treatment should be excluded.
b. Patients who have been currently diagnosed with major depressive and/or generalized anxiety disorders, as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria should not be included (54).
c. Patients suffering from a substance use disorder, as defined by DSM criteria (54), should be excluded.

Comment:

a. See section 1.3.2 on comorbid conditions in IIH.

1.2. Trial Design

Well-designed RCTs are widely regarded as the least-biased research design for evaluating new health technologies and therapies. Diseases may have different characteristics based on the participant's background or geographical location, hence why multicenter trials may deliver results that are more applicable globally.

1.2.1. Masking.

Recommendations:

a. Phase II and III efficacy trials of therapies for IIH should use a double-blind design and with parallel group comparison.
b. Phase II and III surgical trials for IIH should mask the investigators where appropriate.
c. Successful masking should be assessed at the end of the study for both patients and investigators involved in a trial (see masking assessment).

Comments:

a. Drugs intended for IIH can only be reliably evaluated in randomized, double-blind, placebo-controlled trials.
b. Masking may not be required in long-term safety trials.
c. Sham surgeries or comparative surgical trials should mask the investigators where possible. Data and laboratory analysis should be performed by masked investigators. Trial treatment and placebo should be administered in an appropriate format that allows maintenance of blinding.
d. Typically cross-over studies risk unmasking and should generally be avoided.

1.2.2. Placebo.

Recommendations:

a. Therapies under evaluation for IIH ideally should be compared with placebo in cases of IIH without fulminant disease (Table 4) in which the potential for visual loss with placebo is considered to be negligible.
b. In cases of fulminant IIH and/or for surgical procedures the use of placebo is unethical and cannot be recommended.
c. When two presumably active treatments are compared, a placebo control ideally should be included for assay sensitivity.

Comments:

a. The placebo effect is a genuine psychobiological phenomenon that affects the results of clinical trials across many conditions (55).
b. The placebo effect has been studied in primary headache disorders and been noted to affect over 25% of individuals with respect to acute headache relief, with 6% becoming pain free. In addition, up to 25% of patients in such studies may have experienced an adverse event from placebo (56,57).
c. Use of a placebo arm in the setting of carefully monitored clinical trials of consenting subjects outweighs the risk of approval of ineffective interventions.
d. Given the significant risk of permanent visual loss in IIH, the requirement for the use of placebo should be restricted to trials of the milder spectrum of IIH only, with a protocol that includes careful and frequent ophthalmic monitoring.

1.2.3. Randomization.

Recommendation:

a. Subjects enrolled in parallel-group trials should be randomized at the entry to the trial, except when considering adaptive randomization.

Comment:

a. True randomization is essential to avoid bias and, in large trials, to contribute to group matching. Block randomization using varying block sizes (e.g., block sizes of two, four, six, etc.) may be helpful in preventing investigators or participants from guessing treatment assignments.

1.2.4. Stratification.
Recommendation:

a. Stratification should be considered when an imbalance between the treatment groups or an important factor may influence the results of a trial.

Comments:

a. Randomization alone may not ensure full comparability among subjects in different treatment groups, especially in smaller trials, and stratified randomization is sometimes used to circumvent potential imbalances.
b. The Committee for Medicinal Products for Human Use recommends that stratification variables usually be included as covariates in primary analyses, regardless of their prognostic value (58).
c. Some considerations for stratification of IIH trials will depend on the intervention and trial design but may include the following variables:

- Duration of disease
- Duration of treated disease
- Use of concomitant headache preventative medication
- Use of ICP lowering medications
- Use of concomitant diuretic medications
- Body weight or Body Mass Index

d. Caution may be required, as if too many variables are stratified for there may be too many sub-groups which may increase the power calculation estimate and/or have a negative effect on the results of the study.

1.2.5. Intention to treat analysis.
Recommendation:

a. RCTs of therapies for IIH should follow the principle of intention to treat, which implies that analyses should include all randomized subjects in the groups to which they were randomly assigned, regardless of treatment received.

Comments:

a. The intention to treat principle should be adhered to when the primary outcome is a variable that measures a change from baseline to any post-dose time point or to the end of the trial.
b. When the primary outcome is defined as a rate of change, and the analysis will therefore imply a slope or rate of calculation, only subjects who have received at least one dose of the treatment and for whom at least one data point has been recorded should be included.
c. Any per protocol analysis should be defined in the statistical analysis plan prior to initiating the trial.

1.3. Outcome measures

1.3.1. Phase 1 (pharmacokinetic trials).
Recommendations:

a. Endpoints within phase 1 trials will likely report the following outcomes in healthy volunteers and in specific populations:

- absorption
- distribution
- metabolism
- excretion
- Cmax (the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered)
- area under the curve
- half-life in healthy subjects.

b. Drug safety profile includes dose escalation in trials of healthy volunteers, safety signals supporting non-clinical findings and new safety signals in humans.
c. Early phase trials prioritize safety.

Comment:

a. In IIH medication trials, consideration should be given to using healthy volunteer populations with a high body mass index (BMI), as the pharmacokinetics could be different from a person with a normal BMI.

1.3.2. Phase 2/phase 3 and above in IIH.
Recommendations:

a. Early phase, such as phase 2, trials prioritize safety and initial indicators of efficacy.
b. The primary outcome measure chosen depends on the target of the intervention (Table 3).

1.3.3. Clinical trials to evaluate interventions for headache.
Recommendations:

a. The primary outcome for interventions that modify headache should be a headache outcome.
b. Change in headache days; change in moderate to severe headache days; or responder rate should be a primary outcome. From these three endpoints, the two not selected as the primary endpoint should be considered as secondary endpoints.

c. Guidance from the IHS for headache outcome measures have been documented extensively in other guideline documents and should be applied to IIH trials (25–31).
d. Evaluations of efficacy should be based on information obtained from headache diaries. For multinational trials, diary design should be standardized, with translations adapted to the linguistic and sociodemographic characteristics of target population.

Comments:

a. Headache attributed to IIH should be defined according to the diagnostic criteria in the most recent version of the ICHD of the IHS.
b. As people with IIH can demonstrate different headache characteristics each headache type that exists in a given participant should be phenotyped and documented.
c. Tension-type headache and migraine are common and they can co-occur in people with IIH. Up to one third of people with IIH have a prior history of migraine (5,37) and nearly half of people with IIH have a family history of migraine (18).
d. Consideration should be made as to whether participants with a past history of chronic migraine or chronic tension-type headache can be included.
e. Participants with a concurrent history of chronic migraine or chronic tension-type headache at the time of IIH diagnosis and in whom preventative medicines were started prior to their diagnosis of IIH should be excluded.
f. Those with post-IIH persistent headache may have both migraine-like and tension-type- like characteristics to their headache phenotype (5,59,60).
g. Medication-overuse headache (MOH) due to frequent use of analgesics should be defined by the criteria of the most recent version of the ICHD of the IHS.
h. Regular use of analgesic medications is recorded in up to half of IIH patients depending on the study and there is a high burden of opiate use (5,61). Both of which are likely due to the lack of targeted licensed treatments for IIH (60).
i. Exclusion of people with MOH may restrict the eligible population for recruitment therefore MOH could be permitted if stratified for or could be dealt with by using the estimand intercurrent framework (see 1.5.3. Standard statistical methods).
j. Analgesic usage should be recorded daily.
k. The responder rate is calculated as a percent reduction from baseline in the number of headache days or number of moderate or severe headache days in each treatment period (31). Specific responder rate targets must be prospectively defined.
l. When considering headache diaries in IIH, trials investing acute disease or surgical intervention should consider a reduced headache diary or a calendar, such as a 7-day calendar, as it is unethical to withhold treatment in these two acute scenarios.

1.3.4. Clinical trials to evaluate interventions for vision.

Recommendation:

a. The primary outcome for interventions that modify visual function should be a visual outcome.

Comments:

a. Visual outcomes that can be considered are detailed in Table 3.
b. Visual outcomes can be split into functional and structural outcomes.
c. The most commonly used visual outcome is the Humphrey visual field mean deviation. It has several challenges as it dependent on both the technician and patient performance and is prone to variability and inaccuracy with up to one in five people having a performance failure (62,63). Many trials allow multiple attempts to allow for familiarization and learning (63,64).
d. There is currently no consensus to the accepted level of improvement in mean deviation that is considered to be a clinically meaningful change in IIH. While the IIH treatment trial (IIHTT) observed a change in the mean deviation of 0.71 dB that was associated with significant improvement in visual quality of life and the short form 36 physical and mental component summary scores, papilledema and lumbar puncture opening pressure, it has yet to be replicated in other studies.
e. Optical Coherence Tomography (OCT) imaging now provides multiple structural outcomes and is a valuable clinical tool used globally in ophthalmology clinics for the diagnosis and longitudinal monitoring of papilledema. It is a rapid, reproducible, non-invasive, and a highly adaptable technology (1,22). Measures have been shown to correlate well with ICP in the setting of RCT participants (65).
f. There is currently no recommended accepted level of improvement in OCT measures that is considered to be a clinically meaningful change in IIH.

1.3.5. Clinical trials to evaluate interventions for ICP.

Recommendation:

a. The primary outcome for interventions that modify ICP should be ICP.

Comments:

a. When the measurement is taken it should be time-stamped, as timing can influence symptoms and signs.
b. The most common method of ICP measurement in IIH remains the opening pressure at time of lumbar puncture, with several well documented side effects (66,67).
c. As there is high variability in the measure of opening pressure at lumbar puncture, the procedure should be standardized (42).
d. The timing of lumbar puncture can impact the baseline headache diary assessment (67).
e. Telemetric ICP monitors are available commercially and may provide accurate ICP measurements that can be measured at predefined time points. Invasive Continuous ICP monitors that have been previously used in an IIH trial are not currently available commercially (43).
f. Intracranial ICP monitors by cables (often termed ICP bolt) can be used in-hospital or out of hospital for a few days, mostly for diagnostic purposes (68). They may not be suitable for clinical trials depending on the duration of the study.

1.3.6. Clinical trials to evaluate interventions for symptoms of IIH.
Recommendations:

a. The primary outcome for interventions that modify symptoms of IIH could be the most bothersome symptom.
b. The most bothersome symptom endpoint should be selected just prior to randomization and measured on a binary scale (present or absent).

Comments:

a. Defining a most bothersome symptom can be useful in trials in diseases with many different system symptoms like IIH.
b. The use of the most bothersome symptom as a trial endpoint is an alternative to requesting demonstration of a positive treatment effect on all the IIH-associated symptoms.
c. In general, most bothersome symptom requires larger sample sizes due to the need to consider the frequency of the symptoms. It is normally employed in trials involving acute headache therapy.
d. Use of a time-locked recording device (e.g., an electronic diary) to record the most bothersome symptom throughout the duration of the trial is recommended.

1.3.7. Clinical trials to evaluate surgical interventions for IIH.
Recommendations:

a. A specified indication for the aim of the surgical procedure should be stated.
b. Neurosurgical interventions are not recommended for modification of headache (1,22,69).
c. Intended surgical outcomes should be directed at the same outcomes as medical interventions.

Comments:

a. Assessments of surgical procedures in IIH remain limited by the lack of consensus on how to best to define outcome measures. Often, complications or failure are used to define the best surgical intervention, particularly when evaluating two or more techniques. Avoiding surgical complications and revisions are not therapeutic goals in themselves.
b. Intraoperative and post-operative adverse events should be separately reported (70).
c. An outcome measure typically refers to the measured variable (e.g., mean deviation), whereas an endpoint refers to the analyzed parameter (e.g. change since baseline in mean deviation). Table 5 details secondary surgical end points that could be considered (71), in addition to the main outcome measures of headache, vision, and ICP measures, in IIH trials.
d. Due to a lack of licensed treatments and the paucity of RCTs in IIH, there is no current consensus on the definitions of "medically refractory", "drug-resistant" or "medically intractable".

1.4. Secondary endpoints

1.4.1. Patient reported outcomes. Quality of Life is known to be affected by IIH (7–9), in particular, visual quality

Table 5. Secondary surgical end points that could be considered, in addition to the main outcome measures of headache, vision, and ICP measures in IIH trials.

Rate of technically successful procedures
Time to 1st failure of the intervention
Major complications identified according to the validated and widely used Clavien-Dindo classification. Dindo et al., 2004 (71)
Numbers of adverse and serious adverse events
Rate of rescue procedures
Rate of cross over to other arm (in a trial with two interventions, where one may not be standard of care such as a trial comparing CSF shunting with neurovascular stenting)
Rate of failures (evidenced by recurrent disease activity)
Frequency of revision
Reintroduction of IIH medications
Calculated 30-day readmission rate
Number of IIH related admissions

of life is known to be affected by IIH (8). There are two broad approaches to interpretation of quality-of-life changes in clinical trials: anchor-based and distribution-based. Anchor-based are those that rely on the distribution of changes and the effect size. Distribution-based are those that use an external anchor, such as patient judgments of change. Health-status questionnaires are routinely used in RCTs and are critical to fully understand overall treatment effectiveness and to establish the benefit of a given intervention over the standard of care. However, changes in scores on these tools may be difficult to interpret. The statistical significance of a change in any given score may be due to the sample size and may not indicate that the observed change is important.

Recommendations:

a. Ideally validated, disease-specific health-related quality of life and disability instruments should be secondary endpoints (72,73).
b. Validated quality-of-life tools should be used (Table 6) (74–100).
c. Visual quality of life tools also should also be used, where appropriate (Table 6).
d. Best practice would be to define the minimum change in scores on health status questionnaires that are considered important by patients or their clinicians *a priori*.

Comments:

a. There is no IIH-specific quality-of-life measure yet developed.
b. There are two approaches to defining the minimum change: using an external reference e.g., a two-day change; or using distribution method such as standard deviation change.
c. It should be noted that the Unites States FDA guidance recommends anchor-based methods and in some circumstances distributional methods (101).
d. The Patient Global Impression of Change scale (PGIC) can be used to evaluate subject satisfaction as a secondary endpoint (93).
e. A high proportion of people with IIH report migraine-like headaches (5,37,59). Therefore, the migraine validated quality-of-life tools may also be useful to deploy.
f. Using tools that look over a short disease duration may be more appropriate for trials that involve acute cases. For example, the Migraine Functional Impact Questionnaire (MFIQ) evaluates the past seven days (82,83) compared with the Migraine Disability Assessment (MIDAS) questionnaire (86) evaluating over a four-week period.
g. Tools that have been deployed in other migraine trials may be suitable for selection to allow for a comparison of improvement or lack thereof. These may include Migraine Disability Assessment questionnaire (86), The Headache Impact Test – (HIT 6) (89,90) or the headache under-response to treatment (HURT) questionnaire (91) (Table 6).
h. Some tools require a licensing such as the HIT-6 (86,87).

1.4.2. Considerations of confounding conditions that may affect the chosen end points in IIH clinical trials.

Recommendations:

a. Depending on the trial, people with confounding conditions may need to be excluded from recruitment or the condition stratified for at randomization.
b. Depression and anxiety levels should be recorded at the time of randomization and at the end of the double-blind treatment period.
c. Validated scales for depression and anxiety should be used.

Comments on depression and anxiety

a. Depression and anxiety have been noted to be frequent in people with IIH (102–104). A recent study has suggested depression and anxiety burden in IIH is higher than in the general population, but not more common in IIH as compared to migraine. This may indicate that presence of headache as a symptom or migraine may be a potential driver for comorbid depression and anxiety in IIH (61).
b. People with depression and anxiety diagnoses can be included if their symptoms are mild or moderate, properly treated and stable and if their mental status is monitored during the trial. Where there is doubt a professional opinion from a psychiatrist may be required.
c. Validated scales for depression include: Patient Health Questionnaire-9 (PHQ-9) (80), Beck Depression Inventory (BDI) (81), Hospital Anxiety and Depression Scale (HADS) (76).
d. Validated scales for anxiety include the Hospital Anxiety and Depression Scale (HADS) (72), State-train Anxiety Inventory (STA-I) (78), and the Generalized Anxiety Disorder (GAD-7) can be used (79).

Comment on psychiatric disorders:

a. In addition to depression and anxiety, people with IIH may have co-existing mental health diagnoses such as personality disorder, substance abuse, schizophrenia and bipolar disorder (104,105). People with IIH may be at risk of suicide and this has been

Table 6. Quality of life tools that could be deployed in an IIH RCT [74–100].

Quality of Life tool	Comments
Visual related quality of life tools	
25-Item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) (74)	Visual Quality of Life in IIH has been documented by the NEI-VFQ-25, relative to other neuro-ophthalmic conditions (8).
10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 (75)	The 10-Item Neuro-Ophthalmic Supplement demonstrates a capacity to capture self-reported visual dysfunction beyond that of the NEI-VFQ-25 alone.
Anxiety and depression tools	
Hospital anxiety and depression score (76)	HADS is comprised of 14 questions which assess levels of depression and anxiety. In a review of 747 studies found that HADs performed well in assessing severity of anxiety disorders (77). It takes 2–5 minutes to complete.
State-Trait Anxiety Inventory (STAI) (78)	The STAI is a psychological inventory consisting of 40 self-report items on a 4-point Likert scale. The STAI measures two types of anxiety which are state anxiety and trait anxiety. Higher scores are positively correlated with higher levels of anxiety.
Generalized Anxiety Disorder (GAD-7) (79)	The GAD-7 is seven item anxiety scale.
Patient Health Questionnaire (PHQ) 9 (80)	The PHQ-9 is a self-administered nine item depression severity tool.
Beck Depression Inventory (BDI) (81)	The BDI is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression.
Headache specific quality of life tools	
Migraine Functional Impact Questionnaire (MFIQ) (82,83)	MFIQ is a 26-item self-administered instrument for the assessment of the impact of migraine on physical functioning, usual activities, social functioning, and emotional functioning over the past 7 days.
The Migraine-Specific Quality (MSQ) of Life questionnaire (84,85)	MSQ version 2.1 has 14 questions and 3 domains: role function restrictive, role function preventive and emotional functioning. This is recommended for evaluating the change in quality of life related to episodic migraine.
Migraine Disability Assessment questionnaire (MIDAS) (86)	The MIDAS questionnaire was originally validated using a 3-month recall period. Forms using 4-week recall have now been developed and have been used in clinical trials (87).
Migraine physical function impact diary (MPFID) (88)	The MPFID was developed to measure the impact of migraine on physical functioning based on themes raised in concept elicitation interviews with adults with migraine.
Headache impact test (HIT)-6 [Hit-6] (89,90)	The HIT-6 was developed to measure a wide spectrum of the factors contributing to the burden of headache. It consists of six items: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.
The headache under-response to treatment (HURT) questionnaire (91)	An expert consensus group formulated HURT through item development and item reduction using item-response theory. It was validated across two different clinical settings (Europe and Saudi Arabia).
General quality of life tools	
Short form -36 (SF-36) (92)	A number of studies in IIH have utilised the SF-36 (7–9,13,24). The individual scores may be more sensitive in IIH (e.g. role physical, role emotional, pain) than the composite global scores (13,16).
The Patient Global Impression of Change scale (PGIC)(93)	The PGIC is an anchor for minimally important change.
The Patient-Reported Outcomes Measurement Information System (PROMIS)	Pain Interference Scale short form 6b is a 6-item instrument. It measures the level of pain interference on enjoyment of life, ability to concentrate, day to-day activities, enjoyment of recreational activities, doing activities away from home, and socializing with others (94).
The Functional Impairment Scale (FIS)	FIS is a four-point scale that assesses functional status and the intensity of impairment during daily activities (28,30).
Health economics related quality of life	
EQ5D [95]	The EQ5D is employed for health technology assessments and cost effectiveness (96,97). In isolation it may lack sensitivity of other tools for IIH as a quality of life measure but has been used in one RCT (97,98). EQ5D [EuroIqoL Group 1990] needs a license for use (99,100).

documented in over 40% deaths in a United States IIH Registry (106). See section 1.1.8 Comorbidities.

Comments on obstructive sleep apnea (OSA):

a. A co-morbid relationship between IIH and OSA is well described. Nearly 50% of people with IIH and BMI $\geq 35\,kg/m^2$ fulfil the diagnostic criteria for OSA. In the clinical setting, the most sensitive screening tool to identify OSA risk in IIH was the STOP-BANG questionnaire. Treating OSA in patients with IIH may improve papilledema (107,108). Polysomnography is required to confirm OSA.
b. Presence of OSA may influence the visual and ICP endpoints.
c. Patients with this diagnosis can be included, if their symptoms are actively managed and may need to be accounted for at statistical analysis.
d. Where a person has untreated or unstable OSA it should be considered an exclusion to entry to the study. Where there is doubt a professional opinion from a respiratory sleep expert may be required.

Comments on cognitive performance:

a. Disturbances of cognitive performance have been formally noted as part of the IIH clinical phenotype (109). Studies have shown deficits in key areas such as memory, learning, visuospatial skills, concentration, language and executive function (109–112). In particular, deficits in reaction time and processing speed have also been demonstrated (113). Cognitive dysfunction has recently been shown to be reversible, both acutely after lumbar puncture and over time. Importantly, these authors also documented that cognition adversely impacted the visual field performance, which is often a key outcome measure in IIH trials (113).
b. There are a number of potential factors that have been shown to influence cognitive function and that are likely to be relevant in IIH. These include obesity and the resulting pro-inflammatory state, headache, depression, sleep apnea, and hormonal dysregulation (113).
c. If cognition is required to be evaluated then validated tests should be used.

Comment on polycystic ovarian syndrome (PCOS):

a. A higher portion of people with IIH have co-existing PCOS (114,115). This has been confirmed in a population study and people with IIH were compared with those with migraine or a general population without migraine (114).
b. Patients with this diagnosis can be included if their symptoms are actively managed, stable (for >3 months) and may need to be accounted for at the statistical analysis.

Comments on optic atrophy:

a. In a trial with visual outcomes as key end points, optic atrophy should be excluded.
b. Optic atrophy is defined as a pale optic nerve on clinical examination (fundoscopy).
c. The global retinal nerve fiber layer measurement as determined by OCT imaging may be used to define optic nerve damage that could be used as an exclusion criterion. There is no consensus on what level of the global retinal nerve fiber layer measurement is defined as optic atrophy.

1.4.5. Adverse events.

Recommendations:

a. Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.
b. Adverse events (AEs) should be reported separately for the intervention and placebo arms.
c. If a withdrawal from the trial is secondary to an AE (whether it is unrelated or related; expected or unexpected), it should be reported.

1.4.5.1. All adverse events.

Recommendations:

a. AEs can be encountered in participants receiving investigational products. The AEs should be recorded.
b. All AEs and special reporting situations, whether serious or non-serious, should be reported.
c. Serious adverse events (SAEs), including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, also should be reported.
d. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported.
e. Disease-related events and disease-related outcomes that relate to the cause of death of a participant in a study within 12 weeks of the last study intervention, whether or not the event is expected or associated with the study intervention, should be considered an SAE.
f. In addition, safety information that is spontaneously reported by an investigator beyond the time

Table 7. Definition of the expectedness of a serious adverse event and the relatedness (causality) of the SAE.

Category	Definition of serious adverse event	
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the trial protocol.	..
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.	..
Category	Definition of serious adverse event	
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

frame specified in the trial protocol should be evaluated.

1.4.5.2. Assessment of expectedness. The following categories, as outlined in Table 7, should be used to define the expectedness of the SAE.

1.4.5.3. Assessment of relatedness. The following categories, as outlined in Table 7, should be used to define the relatedness (causality) of the SAE.

1.5. Statistics

Recommendations:

a. A general description of the statistical methods to be used to analyze the efficacy and safety of clinical trial interventions should be stated *a priori,* and specific details should be provided in a Statistical Analysis Plan (SAP).
b. The statistical hypothesis and definition of the primary end point should be stated, and a sample size determination should be published.

Comments:

a. Repeated measures of outcomes could be considered to increase power, particularly in a rare disease such as IIH. This requires a suitable analysis method to handle the serial correlation in outcomes, like hierarchical regression.
b. To avoid mean reversion, it is recommended not to use screening measurements as baseline values when using repeated measures. Instead, it is recommended to use a separate assessment for baseline values.

1.5.1. Hierarchy of endpoints. Recommendations:

a. All endpoints need to be defined in the protocol.
b. Hierarchy of endpoints may be adopted for trials investigating the efficacy of interventions for IIH.

Comment:

a. Creating a hierarchy of endpoints reduces the risk of type 1 error.

1.5.2. Sample size calculation.
Recommendations:

a. A calculation of the optimum number of participants required to be ethical and provide scientifically valid results should be stated in advance.
b. A feasibility pilot study may be required to determine the sample size.

Comments:

a. It is neither practical nor feasible to study the whole population in any study. Hence, a set of participants is selected from the population, which is less in number (size) but adequately represents the population from which it is drawn so that true inferences about the population can be made from the results.
b. To avoid bias in interpreting results, the sample size should be determined before the start of a clinical study.
c. If the study is underpowered (too few subjects in a study) the study then may not be able to detect the difference among trial arms.
d. If the study is overpowered (too many subjects than required), more participants are subjected to the risk

of the intervention, which is unethical and wastes resources.
e. If the study population is biased towards a particular spectrum of the disease (e.g., mild versus severe visual loss) the results cannot be generalized to the population as the sample will not represent the whole disease spectrum.

1.5.3. Standard statistical methods.

Recommendations:

a. Randomized controlled trials in IIH should follow the principle of intention-to-treat whenever possible to aim for the highest class of evidence.
b. The statistical analysis plan should be included.
c. An alternative analysis plan should be included if the distribution of data does not meet assumptions of initial planned analyses.
d. Data primarily should be summarized using descriptive statistics. Continuous variables should be summarized using the number of observations, mean, standard deviation, median, interquartile range, minimum and maximum, as appropriate.
e. Ordinal variables such as categorical values should be summarized using the number of observations and percentages as appropriate.
f. The estimand framework has been recommended for use in clinical trials (116).

Comments:

a. Modern statistical approaches including hierarchical regression for repeated measures analysis may be helpful to improve the power of the trial in a rare disease, such as IIH, where there is a limited pool of patients feasible to recruit.
b. The estimand summarizes what the outcomes would be in the same patients under different treatment conditions. The framework consists of the following five attributes: treatment, population, variable, population-level summary, and handling of intercurrent events (ICEs) (116–118). The attributes must be defined in advance, allowing design of a trial to estimate treatment effect.

1.5.4. Missing data reporting.

Recommendations:

a. All IIH trials should report how they have minimized missing data and what strategy they have used to deal with missing data.
b. Methods for handling missing data must be described.
c. If multiple imputation methods are used they must be described.
d. Last value-carried-forward is no longer the recommended method.

Comments:

a. Missing data are always going to occur despite best efforts for minimization. In an intention-to-treat analysis, all randomized participants have outcomes assessed and are analyzed in the group in which they were randomized (regardless of the actual intervention received). However, if participants drop out or miss visits, the intent-to-treat conclusions can be compromised (119).
b. The prevention and treatment of missing data in clinical trials discusses strategies to limit missing data in trial design and the multiple methods employed to deal with missing data (120).

1.6. Trial registration

Recommendation:

a. Prior to initiation, all clinical trials should be preregistered in a register acknowledged by regulatory authorities.

Comment:

a. Clinical trial registers such as clinicaltrials.gov, European Union Drug Regulating Authorities Clinical Trials (EudraCT) database (eudract.ema.europa.eu), clinicaltrialsregister.eu, or a similar regional or national official database should be used.

1.7. Recruitment

Recommendations:

a. Investigators should recruit widely from the population expected to use the treatment being evaluated.
b. Subject participation in previous trials for IIH should be limited to two prior trials and recorded and presented in the publication.
c. Recruitment strategies should be disclosed in the publication.
d. A qualitative recruitment evaluation could be conducted as a Study Within A Trial (SWAT) within the first part of recruitment to the clinical Trial (host trial) to explore in depth the feasibility, acceptability, and appropriateness of the trial processes for participants and healthcare professionals.

Comments:

a. For example, as long as they meet eligibility criteria, all individuals being treated for IIH at specialty

clinics and primary care facilities should be considered for enrolment in clinical trials.
b. The inclusion of people who habitually participate in IIH clinical trials should be discouraged, to avoid bias.
c. It is recommended that investigators establish a database of the number of IIH trials of any kind in which a particular subject has participated in the two years preceding a clinical trial.
d. A SWAT evaluation is helpful in complex trials and will help develop optimum recruitment strategies. This pragmatic qualitative recruitment evaluation is aligned with the Medical Research Council (MRC) framework for evaluation of complex interventions (121).

1.8. Publication

Recommendations:

a. Publication of trial results is necessary and should include all primary and secondary efficacy endpoints and all safety data, whether positive or negative.
b. Standardized reporting guidelines should be used for clinical trials.

Comments:

a. Before any trial-related activities are initiated, a Trial Steering Committee (TSC) should agree on timelines for publication and, if possible, include details in the protocol.
b. At the initiation of the trial or prior to the end of recruitment, a design paper may be published.
c. At the close of recruitment, a baseline-data publication may be considered and published.
d. Authorship of trial-related publications should be based on the criteria of the International Committee of Medical Journal Editors (122).
e. The Consolidated Standards of Reporting Trials (CONSORT) statement provides a minimum set of 25 items to be reported for all randomized trials. The original Consolidated Standards of Reporting Trials (CONSORT) statement published in 1996, was in response to inadequate reporting of randomized controlled trials being associated with bias in the estimation of treatment effect (123,124).

1.9. Conflicts of interests

Recommendation:

a. To maintain the credibility of a trial, authors must declare their conflicts of interest.

Comments:

a. A conflict of interest exists whenever professional judgment concerning a primary interest (e.g. subject well-being or the validity of research) may be influenced by a secondary interest (e.g. financial relationship to a trial sponsor). Financial relationships that represent potential conflicts of interest include employment, consultancies, research grants, fees and honoraria, patents, royalties, stock or share ownership, and paid expert testimony. Investigators should avoid agreements with sponsors, both for-profit and non-profit, that restrict access to trial data, limit its analysis and interpretation, or interfere with the independent preparation and publication of manuscripts.

b. Conflicts of interest also need to be disclosed for the investigator's immediate family (partner or spouse and offspring).

2.0. Independent data safety monitoring

Recommendation:

a. An independent Data Safety Monitoring Committee (DSMC), also named Data Safety Monitoring Board (DSMB), is recommended for all clinical trials.

Comment:

a. The DSMC should monitor safety data as an ongoing process in a clinical trial. The DSMC should have predefined stopping rules for feasibility, futility, and safety. Independent interim analysis by the DSMC should be considered for assessment of the pre-defined stopping rules.

2.0.1. Trial Steering Committee for industry-sponsored trials.

Recommendation:

a. For industry-sponsored trials, the formation of a TSC comprised of academics, statisticians, and (if appropriate) company representatives is recommended.

2.0.2. Trial Steering Committee investigator-initiated trials.

Recommendation:

a. For investigator-initiated trials (i.e., developed and sponsored by independent investigators or academia), a TSC is not necessary, but is best practice.

Comment:

a. Whether or not a TSC is formed, investigators and sponsors are responsible for all aspects of a clinical

trial, including conception, design, operational execution, data handling, data analysis and interpretation, subsequent reporting and publication, and compliance with all local laws and regulations.

3. Post-approval registries

Recommendation:

a. The IHS recommends post-approval product registries (i.e., prospective open-label observational studies) to evaluate the use of newly approved treatments in clinical practice (125).

Comment:

a. Registries generate real-world data on long-term efficacy, tolerability, and safety. They also measure compliance and adherence. Registries for treatments also include individuals with relevant coexistent and comorbid diseases who were excluded from clinical trials on that basis.

4. Public and patient involvement

Recommendation:

a. Public and patient involvement and engagement (PPIE) should be part of all IIH clinical trials.

Comments:

a. PPIE plays an important role in the development and delivery of successful trials. It allows both patients and clinical researchers to understand the needs of one another and helps to ensure that the clinical trial is fit for purpose.
b. Increasing the accessibility of PPIE in health research for people from diverse backgrounds is important for ensuring all voices are heard and represented.
c. The public and patient role should include, but not be limited to, helping define the most relevant research question and trial outcomes; designing a trial appropriate to the needs and lifestyle of the patients; developing accessible and useful participant materials; conducting the trial in a participant friendly way; and dissemination of the trial results to maximize and awareness and ensure the adoption of trial results in clinical practice.
d. Various countries have guidance on public and patient involvement in research. For example the Responsible Research and Innovation (RRI) is a European tool kit (European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 61239) (126).
e. There is a disease specific priority setting partnership which was funded by the United Kingdom (UK) charity, IIHUK. The James Lind Alliance, a UK National Institute for Health Research-supported initiative, IIH priority setting partnership identified existing gaps in knowledge that matter most to key stakeholders (patients, carers and clinicians) and ranked them to recommend the prioritization to funders and researchers (21).

5. Health economic analysis

Recommendation:

a. A health economic analysis could be made alongside clinical trials in IIH.

Comments:

a. Clinical trials evaluating medicines, medical devices, and procedures now commonly assess the economic value of these interventions. This information helps regulatory and reimbursement bodies who use this evidence of economic value alongside clinical efficacy to create policy. All health care resource use should be recorded, and the outcomes assessed using 'natural units' (e.g., change in vision, as measured by the visual field mean deviation) to form a cost-effectiveness analysis.
b. The incremental cost-effectiveness ratio of an intervention compared with an alternative (such as standard of care) can be calculated and is the difference in costs divided by the difference in outcomes.
c. The incremental clinical benefits, measured as Quality Adjusted Life Years (QALYs) also forms a cost-utility analysis.
d. Clinical endpoints that focus on the impact of a treatment on how a patient feels, functions, and survives are the most useful for economic evaluation.

Methodology used for the use of these guidelines

A detailed search of the scientific literature was performed. This included all English language papers on PubMed, Cochrane and Google Scholar between inception until 1 December 2022. The search strategies combined free-text and controlled vocabulary terms for IIH. Key words included: CONSORT; intracranial pressure; idiopathic intracranial hypertension; guidelines; headache; missing data; obesity; outcome measure; papilledema; pseudotumor cerebri; randomized control trial; vision and weight loss.

Three virtual meetings of the IIH Trial Guideline Subcommittee (TGS) took place to present the prior clinical trials and discuss outcomes that are important in this disease. The present guidelines were first drafted by the chairs of the Subcommittee and then presented to the entire Subcommittee. The document then was revised several times by members of the *ad hoc* subcommittee (e.g., bespoke meeting to discuss PROs). It was further revised based on the comments of the IIH subcommittee and IIH UK, a patient charity, by the writing committee. It next was sent for review to members of the IHS Standing committee, and revised further until an agreement was reached and the pre-final version was supported by all. This version was submitted to various stakeholders, including pharmaceutical and devices manufacturers, soliciting and incorporating their feedback on the expert analysis. IHS members then were invited to comment on the IHS website before final approval of the document by the IHS Board of Trustees was given. This process was as agreed by the IHS board.

The main purpose of this guideline was to highlight issues inherent in drug and surgical trials in IIH and to encourage investigators to tackle these problems during the design phase of the trial to improve the quality of controlled clinical trials. Recommendations are based on the clinical experience and research experience of the committee members.

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Declaration of conflicting interests

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SPM has received honoraria for speaker events from Heidelberg engineering; Chugai-Roche Ltd and Teva. Honoraria for advisory boards for Invex Therapeutics and Gensight. Consultancy fees Neurodiem and Invex Therapeutics. Research funding from the UK Space Agency.

HCD received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Lilly, Novartis, Pfizer, Teva, Weber & Weber and WebMD. The German Research Council (DFG), the German Ministry of Education and Research (BMBF) and the European Union support headache research by HCD. HCD serves on the editorial boards of Cephalalgia, Lancet Neurology and Drugs. HCD is a member of the Clinical Guidelines Committee of the German Society of Neurology and of the Clinical Trials Committee of the IHS.

NRM has received honoraria from the advisory board for Invex Therapeutics

CKMC reports no conflicts of interest.

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RHJ has received honoraria for oral presentations from Lectures for Pfizer, Eli-Lilly, ATI, Merck, TEVA, Novartis, Lundbeck and Allergan. She is investigator in clinical trials with ATI, Eli-Lilly, Novartis and Lundbeck and Director of Danish Headache Center, Lifting The Global Burden of Headache and Founder of Master of Headache Disorders at University of Copenhagen. Received research funding from University of Copenhagen, Rigshospitalet, ATI, Lundbeck Foundation, The Medical Society in Copenhagen, NovoNordisk Foundation and Tryg Foundation.

CLF has received consulting fees for Invex therapeutics

PPR has received honoraria as a consultant and speaker for: AbbVie, Amgen, Biohaven, Chiesi, Eli Lilly, Lundbeck, Medscape, Novartis, Pfizer and Teva. Her research group has received research grants from Novartis, Teva, AbbVie, EraNET Neuron, RIS3CAT FEDER, AGAUR, ISCIII; has received funding for clinical trials from Alder, Amgen, Biohaven, Electrocore, Eli Lilly, Lundbeck, Novartis, Teva. She is the Honorary Secretary of the International Headache Society. She is the founder of www.midolordecabeza.org. PP-R does not own stocks from any pharmaceutical company.

KBD is on the data safety and monitoring committee for Invex trial.

RBL reports no conflicts of interest.

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MT reports no conflicts of interest.

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