

**Title: The Incidence of Idiopathic Intracranial Hypertension in Scotland: a SOSU Study**

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This study was supported by the Scottish Ophthalmic Surveillance Unit, through the  
Ross Foundation SOSU study bursary.

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Running title – The Incidence of IIH in Scotland

Word count – 2354

## **Abstract**

**Background** – Idiopathic intracranial hypertension most commonly affects women of childbearing age and usually causes headache and intermittent visual obscurations. Some patients suffer permanent visual loss. The major modifiable risk factor associated with IIH is obesity. Scotland has one of the poorest records for obesity in the western world with a prevalence in 2016 of 29% in the adult population. We aimed to establish the incidence of idiopathic intracranial hypertension (IIH) in Scotland.

**Methods** – All new cases of IIH seen in Scotland were collected over a one-year period. Cases were reported by ophthalmologists through the Scottish Ophthalmic Surveillance Unit (SOSU) and by neurologists directly to the investigators using encrypted NHS emails. An open dialogue was maintained between the investigators and specialist neuro-ophthalmology clinics throughout the year to minimise the risk of underreporting. Cases were defined using the Modified Dandy Diagnostic Criteria.

**Results** – One hundred and forty-four confirmed cases of IIH were reported. One hundred and ten out of 144 patients were female and aged 15-44. The mean BMI in this group was 38.9.

**Conclusions** – The incidence of IIH in Scotland is at least 2.65/100,000. This figure rises to 37.9/100,000 in obese females aged 15-44. This figure is higher than previously published and is probably a result of increasing levels of obesity across the nation. The significant morbidity caused by IIH, in this young population raises the question of whether enough is being done to prevent and treat Scotland's obesity crisis.

**Keywords** – IIH, obesity, BMI

## **Introduction**

Idiopathic intracranial hypertension (IIH) is a syndrome characterised by raised intracranial pressure in the absence of clinical, laboratory and radiological evidence of a space occupying lesion or hydrocephalus. Its aetiology is unknown, however it classically affects young women of childbearing age.<sup>1-3</sup> Diagnosis is made based on the Modified Dandy Criteria<sup>4</sup> and the clinical features, risk factors, natural history and long-term follow-up are well described in the literature<sup>5</sup>. Previous estimates of the annual incidence of IIH is varies from 0.03-2.4 per 100,000, however this varies depending on ethnicity, geographical location, age and sex (see table 1). IIH is more common in women and is predominantly a disease affecting younger adults. The estimated incidence in woman aged 15 to 44 years is 3.5/100,000. The most common symptoms of IIH are headache and transient visual loss. In the majority of cases, IIH is treatable, without impairment of vision in the long term. However, a significant group of patients exist who develop permanent visual loss, which can be rapidly progressive and devastating.<sup>6</sup>

The major modifiable risk factor associated with IIH is body mass<sup>7-10</sup>. The majority of patients with IIH are obese (defined as having a body mass index (BMI) of over 30) with an additional link to *recent* weight gain<sup>11</sup>.

Scotland has one of the poorest records for obesity in the western world with a prevalence in 2016 of 29% in the adult population<sup>12</sup>. We have previously performed a prospective incidence study of IIH amongst the entire population of Fife, an area on the east coast of Scotland with a population of 365,000, and found the incidence to be 3.56/100,000.<sup>13</sup> This is higher than previous studies reporting from similar populations. The prevalence of obesity in Fife is only slightly higher than the national average and did not account for such a high incidence. As a consequence we decided to undertake a nationwide incidence study in Scotland over a period of one year to see if other regions

in Scotland reflected the findings in Fife as well as to describe the demographics of those affected by IHH.

## **Methods**

All new cases of IHH seen by ophthalmologists or neurologists in Scotland were collected prospectively between November 1 2016 and October 31 2017. Cases seen by ophthalmologists were reported via the Scottish Ophthalmic Surveillance Unit (SOSU). SOSU is run by the Royal College of Ophthalmologists, alongside the British Ophthalmic Surveillance Unit (BOSU), to assist with the epidemiological study of rare ocular disorders. It is an active prospective case ascertainment system that engages with all consultant or associate specialist ophthalmologists in Scotland (122 individuals were on the database at the time of data collection) to identify cases of rare eye diseases to provide meaningful data for epidemiological analysis. Each month, every ophthalmologist in Scotland was posted a SOSU reporting card asking if they had managed any new cases of IHH in their practice. When a case was reported, a questionnaire was sent to the notifying ophthalmologist asking for demographic and clinical data on the case, including BMI, medications and postcode. If BMI was not known we asked clinicians to comment on whether they considered the patient to be clinically obese. If the questionnaire was not returned a reminder letter was sent to increase the response rate. Ophthalmologists were also sent a 6 month follow-up questionnaire for each case they reported. An identical system was developed with all neurology departments in Scotland. Neurologists were contacted by secure NHS email and when a case was reported an abbreviated questionnaire was requesting patient age, sex and postcode.

To maximise case reporting from higher volume specialist neuro-ophthalmologists, there was a more open dialogue with the investigators, allowing cases to be reported by email, rather than being restricted to the SOSU reporting cards.

Cases of IIH were defined using the the Modified Dandy Criteria, namely:

- If symptoms and / or signs are present, they may only reflect those of generalised intracranial hypertension or papilloedema
- Intracranial pressure, as measured in the lateral decubitus position, is elevated
- The composition of the cerebrospinal fluid is normal
- There is no evidence of hydrocephalus, mass, structural or vascular lesion
- No other cause of intracranial hypertension has been identified

Ethics advice was sought from the South East Scotland Research and Ethics Service and approval was granted through the Public Benefit and Privacy Panel for Health and Social Care in Scotland.

Population obesity data was taken from the Scottish Health Survey 2016.<sup>12</sup> Data on social deprivation was analysed depending on postcode using the Scottish Index of Multiple Deprivation, also from the Scottish Health Survey 2016. The incidence of IIH was calculated using a Scottish population of 5,424,800.<sup>14</sup>

## **Results**

206 cases were reported to the investigators during the 12-month study period. Thirty of these were excluded, whilst 32 cases were reported by more than one source, leaving a total of 144 cases. The breakdown of these case reports is shown in figure 1. Thirteen cases were incorrectly reported following errors with the SOSU reporting system and so were excluded. Other reasons for exclusion were duplicate reports from the same source (8), cases reported outside the study period (4) and incorrect diagnosis (5).

Twenty-seven of these cases were reported by a neurologist only and therefore only age, sex and postcode was collected. Questionnaires were sent for the remaining 117 cases and 111 responses were received, 106 of which included usable information.

The SOSU card response rate from ophthalmologists each month was 68%, whilst the response rate from neurologists (via email) was 30%.

### Patient demographics

The mean patient age was 27.7 years with a range of 6 year to 63 years. One hundred and ten patients were female and aged 15-44. Eleven patients were under 15 (5 male, 6 female) and 12 patients were over 44 (2 male, 10 female).

### Obesity

Information regarding obesity was reported for 103 patients, whilst BMI was available for 75. Seventy-three out of 80 (91%) females aged 15-44 were considered to be obese. BMIs were reported for 49 patients in this group with a mean of 39.8 (range 17.5 – 107.3). 43 out of 49 had a BMI greater than 29.9, whilst 47 out of 49 had a BMI of greater than 24.9. Five out of 9 children, 5 out of 7 men and 5 out of 7 women over 44 were considered to be obese.

### Social deprivation

The distribution of patients by NHS Board and SIMD data is shown in the figure 2. Vignitile 1 includes the most deprived 5% of the population, whilst vignitile 20 includes the least deprived 5%. When SIMD data was corrected for obesity, our data did not demonstrate an independent link between social deprivation and IHH.

## Medication use

Nine patients were taking the oral contraceptive pill, whilst 6 others were reported as using alternative forms of long-term contraception (3 intrauterine devices, 3 contraceptive implants). Five patients were pregnant at the time of diagnosis. Six patients reported current or recent use of corticosteroids (1 of these cases was thought to be secondary to the use of fludrocortisone) and 4 patients were taking tetracyclines. One patient developed IIH following an infusion of intravenous immunoglobulin to treat chronic inflammatory demyelinating polyneuropathy. Sixty-nine out of 111 were taking no medications prior to their diagnosis.

One-hundred-and-seven out of 111 patients had bilateral optic disc swelling, 2 patients had unilateral swelling and 2 patients had normal optic disc appearances. Further clinical information and data from the 6-month follow-up questionnaire (which was obtained for 103 cases) will be reported in a subsequent article.

## **Discussion**

This prospective study estimates that the incidence of IIH in Scotland is 2.65/100,000. In females aged 15-44 the incidence is 10.7/100,000 and in obese females, aged 15-44 the incidence is 37.9/100,000. These figures are significantly higher than previously published, which may reflect levels of obesity in Scotland. IIH is known to cause significant morbidity, via headache and in some cases irreversible loss of vision. Headache is associated with low mood and along with visual loss leads to significant psychological, social and economic consequences, magnified by the young population that is affected by this condition.<sup>15</sup>

A recent meta-analysis<sup>16</sup> and systematic review of epidemiological studies in IIH highlights significant variability in the incidence of IIH (see table 1) based on

population characteristics, particularly obesity. They describe a paucity in large, high quality epidemiological studies looking at IHH. Very few of the studies they looked at were prospective and when compared to all large studies (population size over 1,000,000) our data for the Scottish population estimates a significantly higher incidence.

The demographics of our study were consistent with the literature, with the majority of cases affecting women, aged 15-44. Mean BMI of 39.8 is also consistent with previous studies. BMI was not recorded for 36 out of 111 cases (33%). The recently published consensus guidelines on IHH identify weight loss as the only disease modifying therapy in typical IHH, advising that BMI should be recorded at all follow-up appointments. Patients with IHH often struggle to lose weight. Regular BMI monitoring in clinic may serve as a reminder and promote discussion about the importance of weight loss in managing IHH, taking emphasis away from the medications that often demand much attention during a consultation but do not in fact modify the course of the disease.

This data adds further weight to evidence from many other medical specialties that Scotland's obesity epidemic is causing significant morbidity, and raises the question about whether enough is being done at a public health level to reverse the trend.

Our study is the first to show that IHH is most prevalent in areas of social deprivation. It is likely that higher levels of obesity in these areas explain this link. Indeed, when we analysed our results, corrected for obesity, social deprivation was not an independent risk factor for IHH. It is interesting to note that the number of cases reported drop off in the 2 most deprived vigintiles. This almost certainly reflects under-



reporting due to lack of engagement with or lack of access to health services in these populations.<sup>17</sup>

Whilst the pathogenesis is not fully understood it is thought that 'prepubertal' IHH and 'secondary' IHH, linked to medication use, are distinct conditions from typical 'weight-related' IHH.<sup>15</sup> Eleven cases of IHH were reported in patients under 15 years-old (male:female = 6:5), although we did not specifically ask if these individuals were prepubertal. The male to female ratio in prepubertal IHH is nearly one, a condition that may not be associated with weight. Of the nine reported cases that included information about obesity, five (55%) were considered to be obese.

The number of cases in our study is not sufficient to reach a conclusion on the role that individual medications play in the pathogenesis of IHH. Nine out of 111 patients (8.1%) were taking the oral contraceptive pill at the time of diagnosis. There is conflicting evidence linking oral contraception and IHH. Recent consensus suggests that similar to pregnancy, it is likely that this relationship reflects the typical age and gender profile of an IHH patient rather than the medication itself.<sup>1,7,8</sup> Five patients (4.5%) were pregnant at the time of diagnosis. As with oral contraceptive use, a seemingly high prevalence of IHH during pregnancy is thought to reflect young, female demographic affected. It is likely that patients diagnosed during pregnancy likely had onset of IHH prior to getting pregnant. Our experience suggests that IHH often stabilises during pregnancy despite stopping treatment.<sup>18</sup>

Of the six patients that reported current or recent use of corticosteroids 2 were male, and one female was over 44. Only one of these patients was obese (female aged 15-44). Secondary IHH has been reported with corticosteroid excess and also with deficiency (such as in Addison's disease) although this link is not established.<sup>15</sup> All four patients that were taking tetracyclines were females, aged between 15 and 44 who were

obese. IIH has been reported in patients taking tetracycline antibiotics in many case reports and in one case-control study, however other prospective studies have failed to confirm this link.<sup>1,8,11</sup> One patient developed IIH following an infusion of intravenous immunoglobulin to treat chronic inflammatory demyelinating polyneuropathy. If these cases are truly linked to medication then they should be considered as secondary IIH, which should be considered differently to weight associated IIH.

It must be true that the true incidence of any condition, with specific diagnostic criteria, that is the subject of a study that relies on case reporting will be equal to or higher than the reported figure. The main reason for this is under-reporting. Response rates from ophthalmologists and neurologists were similar to previous BOSU/SOSU studies and other electronic case reporting studies respectively. By receiving case reports from multiple sources (neurology, ophthalmology and specialist neuro-ophthalmologists) we attempted to minimise under-reporting. Our data shows a significant variation in cases reported depending on NHS board across Scotland. In smaller NHS boards, the population is such that 1 or 2 new cases will significantly change the incidence per 100,000 and so a study period of 1 year does not accurately reflect the incidence. The variation seen between the larger health boards (most noticeable when comparing Lothian and Tayside) probably reflects under-reporting, where busy clinicians fail to report cases they have seen.

The Modified Dandy Criteria were used to define the diagnosis of IIH in our study. In reality the diagnosis is often not straightforward, which is reflected in recently published consensus guidelines.<sup>15</sup> This is further highlighted by Fisayo et al<sup>19</sup> who suggest that IIH is often over-diagnosed, despite the Modified Dandy Criteria. Their retrospective study showed that a significant proportion of patients initially diagnosed with IIH by non-neuro-ophthalmologists (including ophthalmologists, neurologists and

optometrists) did not have IIH, according to the neuro-ophthalmologist. They cited the most common source of error was inaccurate assessment of the optic nerve head, (usually anomalous optic nerves being misinterpreted as papilloedema). Mild optic disc swelling from papilloedema can be a subtle sign and an asymptomatic patient, with normal imaging, can be observed by experienced clinicians, rather than proceeding with an invasive lumbar puncture.

Our study design was such that false positives were unlikely. Eighty-two out of 144 new cases were reported by specialist neuro-ophthalmologists. Six month follow-up data was available for 103 cases, none of whom had their diagnosis revised. We are unable to comment on the diagnostic accuracy of the 27 cases reported by neurology only, however it is likely that most (if not all) of these will have also been seen by an ophthalmologist, with the fact they were reported by neurology only, reflecting under-reporting by ophthalmologists.

Furthermore, in certain cases measuring opening pressure by lumbar puncture can be unreliable. It is important to follow a standard protocol when obtaining an opening pressure, to avoid inaccurate results. LP can be more difficult in obese patients, where bony landmarks are less obvious, anxiety, leading to tense muscles can alter true CSF pressure. If LP opening pressure does not fit the clinical picture, it should be interpreted with caution. For clarity and consistency, elevated opening pressure on LP was an essential part of the inclusion criteria in our study, which may have resulted in underreporting caused by false negatives.

Although our figure of 2.65 cases of IIH for 100,000 of the population is almost certainly an underestimate, it is clear that the incidence of is increasing, alongside increasing levels of obesity throughout Scotland. We have shown that the incidence of IIH in Scotland is at least 2.65/100,000, which rises to 40 per 100,000 in obese young

women. Frustratingly, for most of people IHH should be preventable. Our study is the latest in a long line, showing increased morbidity caused by Scotland's obesity crisis and raises questions about whether we, as a society, are doing enough to prevent and treat this modern epidemic.

This study was supported by the Scottish Ophthalmic Surveillance Unit, through the Ross Foundation SOSU study bursary. The authors have no conflicts of interest to report.

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Table 1. Published Incidence of IIH in the literature

(see separate document for table 1, due to formatting)

Table 2. Patient demographics showing obesity and BMI data

	Number (n=141)	Patients considered to be clinically obese	Mean BMI (range)
Female < 15	6	4/4 (100%)	28.5 (1 reported)
Male < 15	5	1/5 (20%)	20.99 (16.64-16.28)
Female 15-44	110	73/80 (91%)	39.8 (17.5-107.3)
Male 15-44	8	5/6 (83%)	39.0 (28.7-47.9)
Female > 44	10	5/7 (71%)	39.4 (24.2-56.5)
Male > 44	2	0/1 (0%)	n/a

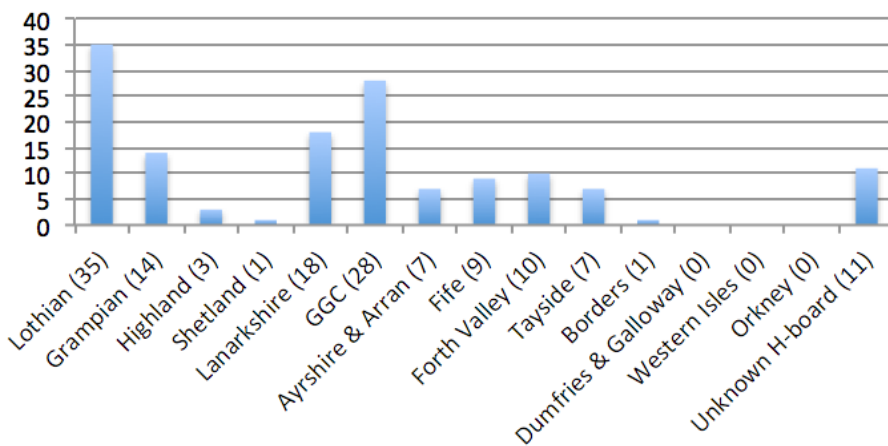
Figure 1. Source of reported new cases of IIIH



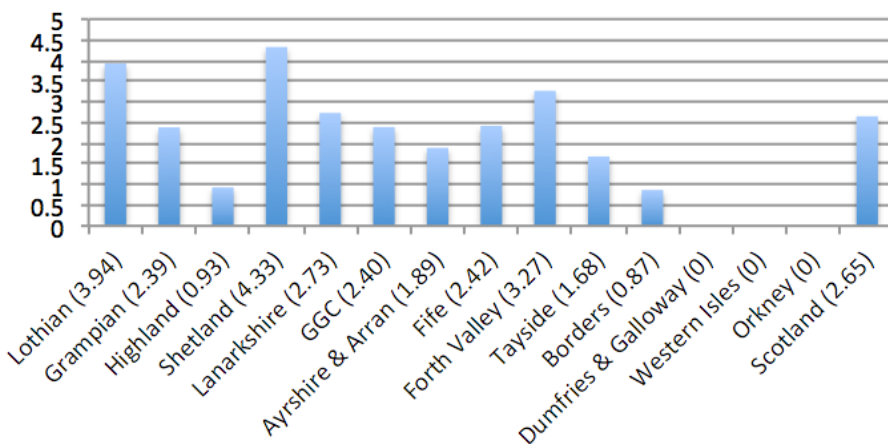


Figure 2. Number of cases of IIH shown by healthboard, per 100000 of population and per SIMD viginitle. Viginitle 1 is the most deprived 5% of the population.

### Number of cases of IIH



### Cases of IIH per 100000 of population



### Cases of IIH per SIMD vigintile

