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REVIEW ARTICLE

Meta-analysis and systematic review of population-based epidemiological studies in idiopathic intracranial hypertension

G. McCluskey[a], R. Doherty-Allan[b], P. McCarron[c], A. M. Loftus[d], L. V. McCarron[e], D. Mulholland[f], F. McVerry[g] and M. O. McCarron[g]

[a]*Department of Neurology, Royal Victoria Hospital, Belfast;* [b]*Ulster University, Derry, UK;* [c]*National Drug Treatment Centre, Dublin, Ireland;* [d]*Aberfoyle Medical Practice, Derry;* [e]*Medical School, University of Cambridge, Cambridge;* [f]*Department of Ophthalmology, Altnagelvin Hospital, Derry; and* [g]*Department of Neurology, Altnagelvin Hospital, Derry, UK*

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Idiopathic intracranial hypertension (IIH) is positively associated with obesity, mostly in young women. The global increase in obesity may influence the burden of IIH. Using the PubMed, Embase, MEDLINE and Web of Science databases, a meta-analysis and systematic review of epidemiological studies of IIH were performed up to June 2017. Temporal changes in IIH incidence were measured, and incidence rates of IIH were correlated with country-specific World Health Organization obesity rates. Prevalence data and shunting rates of IIH were recorded. The quality of epidemiological studies was assessed using the Standards of Reporting of Neurological Disorders (STROND) criteria. In 15 identified studies, there were 889 patients (87% women), mean age 29.8 years. The incidence of IIH ranged from 0.03 to 2.36 per 100 000 per year. The pooled incidence of IIH was 1.20 per 100 000 per year although there was very high heterogeneity (I^2 98%). The incidence rates of IIH were correlated with country-specific prevalence of obesity (Spearman's correlation 0.82, $P < 0.01$). The prevalence of IIH was rarely recorded. A shunting procedure was reported in 8% of patients. STROND criteria were variably reported, median of 26.5 of 43 (range 16–35). IIH is a public health concern as increased obesity prevalence is associated with increased incidence of IIH. A better quality of epidemiological studies is required to improve understanding of IIH and inform health policy for IIH management.

Introduction

There is a pressing need for accurate epidemiology of neurological disorders. High standards of neuroepidemiological reports help not only to provide a record of morbidity and mortality but also to estimate the economic burden of disease and identify healthcare service needs [1]. With an emerging global obesity epidemic [2–4], conditions associated with obesity such as idiopathic intracranial hypertension (IIH) merit particular attention to define their natural history, to generate causal hypotheses and to facilitate implementation of effective public health interventions.

Correspondence: M. O. McCarron, Department of Neurology, Altnagelvin Hospital, BT47 6SB Derry, UK (tel.: +44 287 1345171; fax: +44 287 1611417; e-mail: markmccarron@doctors.org.uk).

Idiopathic intracranial hypertension is a disorder of uncertain aetiology mainly affecting a proportion of young and obese women [5]. Clinical features include headache, which can be very non-specific, transient visual obscurations, diplopia and pulsatile tinnitus [6].

There is a paucity of large detailed epidemiological studies in IIH. It is not clear whether prevention of IIH should be targeted at susceptible individuals such as bariatric surgery groups or directed at the population level. It is also not clear if obesity prevalence is associated with IIH risk. Review data have been mainly limited to simple descriptive incidence rate analyses [5,7]. Assessments of temporal trends in IIH epidemiology have rarely been reported [8]. There has also been a lack of qualitative measurement of neuroepidemiological studies.

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Because neurological diseases are becoming more prevalent, may have subtle presentations and epidemiologically represent a particular challenge, criteria for Standards of Reporting of Neurological Disorders (STROND) have recently been developed as a guideline to improve the reporting of key information for health policy research [1]. The STROND criteria have 15 key items amongst which there are 29 'basic minimum' and 14 'ideal reporting' requirements.

The aim was to meta-analyse and systematically review the epidemiology of IIH and to examine the association with obesity in further detail to identify service and research needs for IIH. As a qualitative measure of our systematic review [9], each study was assessed for completion of the STROND criteria [1].

Methods

Literature search and selection criteria

A literature search of four medical databases (Ovid MEDLINE, Embase, PubMed and Web of Sciences) was performed for all relevant epidemiological studies of IIH from 1960 until 30 June 2017, using keywords or MESH terms (idiopathic intracranial hypertension OR benign intracranial hypertension OR pseudotumour cerebri AND epidemiology OR incidence OR prevalence). The search was restricted to English language reports. The bibliographies of the included studies were searched for additional studies. All population-based epidemiological studies of IIH were included without exclusion criteria in order to facilitate the quality assessment with STROND criteria.

Any of three well-known IIH definitions were acceptable for study inclusion: the modified Dandy [10], Friedman 2002 [11] and revised Friedman 2013 [12] criteria. Studies of paediatric (<14 years) populations were excluded. Our findings are reported as suggested in the guidelines for the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [13].

Data collection

One of the authors (MOM) extracted data from each study according to a piloted proforma. Demographic information on study participants was collected including mean age, sex ratios and weight/body mass index (BMI). Incidence rates and prevalence of IIH and 95% confidence intervals were recorded. The population denominator used for calculation of rates was also recorded. Where this was not stated in the article, attempts were made to determine study population size, e.g. through use of census data in study areas at the midpoint of the study.

For analysing temporal trends in incidence, the middle year point of the study was used. Where available, age and sex-specific incidence were also recorded. Shunting procedure (thecoperitoneal, ventriculoatrial, ventriculoperitoneal, optic nerve fenestration and transverse sinus shunting) rates were recorded. All included studies were independently reviewed by GM to verify data accuracy.

Data analyses

A meta-analysis was performed to calculate the pooled incidence rate. Subgroup analyses were performed on studies based on prevalence of obesity (<10%, 10%–20% and >20%) and on mid-year point of the study (pre-2000 and 2000 and beyond).

Incidence rates of IIH were correlated with country-specific obesity rates as reported by the World Health Organization (WHO) [14]. The midpoint year of the epidemiological study was used with the nearest WHO prevalence data for obesity for the country where the study was performed. Incidence rates were also correlated with midpoint year of study to analyse for temporal trends in IIH incidence.

Forest/funnel plots and meta-analyses were performed using Review Manager version 5.3. In order to perform a meta-analysis, when not reported the standard error for each incidence rate was calculated using the formula $\sqrt{p(1-p)/n}$ (where p is the study population and n is the number of cases of IIH). Pooled estimates were calculated using the random effects model and heterogeneity was measured using I^2. A low heterogeneity value was taken as <25%. As all data were continuous, the inverse variance method was used.

Scatter plots and Spearman's rank calculations were performed using Microsoft Excel Ver. 3. 2013 to determine the correlation between obesity or year of study and IIH incidence. Publication bias was assessed visually using funnel plots.

Quality measurement of epidemiological studies

The STROND criteria were measured as absent or present in each study. Two authors (GM and MOM) scored the studies following review of the explanations of the standards for the STROND criteria [15]. Where disagreement occurred, a consensus decision was determined after further review of the epidemiological publication and discussion.

Results

Literature search

The literature search identified 15 studies of IIH epidemiology from 14 publications fulfilling the inclusion criteria (Table 1 and Fig. 1) [6,8,16–27]. Excluded studies are itemized in the appendix of the MOOSE [13] proforma. Amongst the excluded studies, one study failed to distinguish prevalence and incidence [28] and one study included the same patients in two reports [16,29]; only the larger study was used for analyses [16].

There were 889 patients with a female:male ratio of 6.9:1 (Table 1). The mean age was 29.8 years. Where recorded, shunting procedures were performed in 8.3% of patients (20 of 239).

Incidence rates

The incidence rates varied from 0.03 per 100 000 per year in Japan to 2.36 per 100 000 per year in Northern Ireland (Fig. 2a). Meta-analysis of all 15 included studies showed a pooled incidence of IIH of 1.20 per 100 000 [95% confidence interval (CI) 0.82, 1.57] per year, although there was very high heterogeneity with I^2 of 98%, which limits the interpretation of this result (Fig. 2a). Age- and sex-specific incidence rates were provided for females from 14–17 to 45 years in 11 of the 15 studies. The incidence of IIH in females from 14–17 to 45 years ranged from 0.65 per 100 000 per year in Italy to 10.3 per 100 000 per year in Libya.

For subgroup analysis by study year, studies were divided into midpoint year of study pre-2000 or 2000–2017. As one study spanned the years 1990–2014 and presented separately reported data for pre- and post-2000 incidences, the separately reported incidences were used. The subgroup analysis showed an IIH incidence of 0.84 per 100 000 per year (95% CI 0.48, 1.21) where the midpoint year was pre-2000 and 1.90 per 100 000 per year (95% CI 1.48, 2.32) for studies with the midpoint year from 2000 onwards. There was again high heterogeneity within both subgroups ranging from 83% to 97% (Fig. 2b).

Using the WHO BMI database [14] for the nearest year to the relevant study, the incidence of IIH was positively associated with the national prevalence of obesity (Spearman's correlation 0.82, $P < 0.01$, Fig. 3a). A temporal trend in IIH incidence and year of study was not identified (Spearman's correlation 0.37, $P = 0.19$, Fig. 3b).

Data on obesity prevalence in the study population were available from the WHO database for 13 studies. Subgroup analysis on these studies by obesity prevalence showed an incidence of IIH of 0.14 per 100 000 per year for obesity prevalence <10% (95% CI 0.00, 0.39), 0.77 per 100 000 per year for obesity prevalence 10%–20% (95% CI 0.50, 1.04) and 1.48 per 100 000 per year for obesity prevalence >20% (95% CI 0.98, 1.99) (Fig. 2c). There was still high heterogeneity within all subgroups ranging from 82% to 96%.

Prevalence

There were relatively few data on prevalence of IIH. Prevalence of IIH varied from 5.1 to 14.3 per 100 000 population. One report recorded prevalence as incidence multiplied by duration of study per 100 000 population [23]. Another study recorded hospital attendance of IIH patients in a given year as a measure of IIH prevalence [6]. No study actively confirmed an elevated opening pressure of cerebrospinal fluid as a measure of IIH prevalence (the gold standard).

Publication bias

A funnel plot (Fig. 4) highlighted a lack of small studies showing lower incidence rates, which may suggest publication bias in favour of studies showing a higher incidence.

Qualitative assessment

Both the number of sources of ascertainment and study size have increased in the more recent epidemiological studies of IIH (Table 2 strengths and weaknesses). Reporting of basic items amongst the STROND criteria ranged from 14 to 26 out of 29, median score 21, with no evidence of improvement with year of study (Table 2). Inclusion of recommended items with basic items (total of 43 items) resulted in scores ranging from 16 to 35 and a median score of 26.5. A temporal trend in quality measurements was not identified. Particular reporting deficits in STROND items reported on five or fewer occasions in total included absence of pilot study, rate of hospital admission, types of IIH, assessment of case ascertainment, documented ethical approval, measurement of prevalence, disease burden disability, triangulation, explanation of missing data, and confidence interval calculations.

Discussion

Interpretation of findings

This study has demonstrated that country-specific IIH incidence is associated with national prevalence of

Table 1 Population-based epidemiological studies of idiopathic intracranial hypertension.

Author/year(s) of study	Country	Number	Female:male	Mean age	Duration	Population	Incidence/10^3/year	Females 15/18–45 years incidence	Shunt/ONF rate
Durcan [17]/1984–1985	Iowa, USA	27	24:3	26.7	1 year	2 913 808	0.9 (0.62–1.33)	3.5	
Durcan [17]/1984–1985	Louisiana, USA	48	39:9	28	1 year	4 480 681	1.07 (0.80–1.41)	3.5	
Radhakrishnan [16]/1982–1989	Libya	79[a]	76:3	28	7 years	519 000	2.17 (1.73–2.70)	10.3	2 (2.5%)
Radhakrishnan [18]/1976–1990	USA	9	8:1	27.8	15 years	70 000	0.9 (0.42–1.57)	3.3	
Yabe [19]/1993	Japan	2	1:1	22.5	1 year	Not given	0.03	–	0 (0%)
Craig [20]/1991–1995	Northern Ireland	42	36:6	29	5 years	Not given	0.5	–	7 (17%)
Kesler [22]/1998–1999	Israel	91	85:6	32.3	2 years	597 0000 + 6 035 000/2	0.75 (0.61–0.92)	4.02	
Carta [21]/1990–1999	Italy	10	8:2	36	9 years	400 000	0.28 (0.14–0.50)	0.65	2 (20%)
Kesler [24]/2005–2007	Israel	293	252:41		3 years	14 123 200/3	2.07 (1.44–2.05)	5.49	
Raoof [23]/2007–2008	England	16	15:1	28.1	2 years	Not given	1.56	–	
Contreras- Martin [25]/1999–2009	Spain	61	42:19	35.4	10 years	Not given	1.2	–	5 (8.2%)
Idiculla [26]/2001–2011	Oman	27[a]	20:7		11 years	166 318	1.62 (1.1–2.3)	4.14	
McCluskey [6]/2007–2014	Northern Ireland	45	44:1	29.4	7 years	182 518	2.36 (1.65–3.37)	9.85	4 (9%)
Sundholm [27]/2006–2013	Sweden	83			8 years	Not given	0.65 (0.57–0.73)	1.96	
Kilgore [8]/1990–2014	Olmsted County, USA	56[a]	54:2		24 years	129 222 (2002)	1.8 (1.3–2.2)	6.8	
Total		889	704:102 (6.9:1)	29.8	1–24 years				20 (8.3%)

ONF, optic nerve fenestration. [a]Patients under 14 years were removed from the original report.

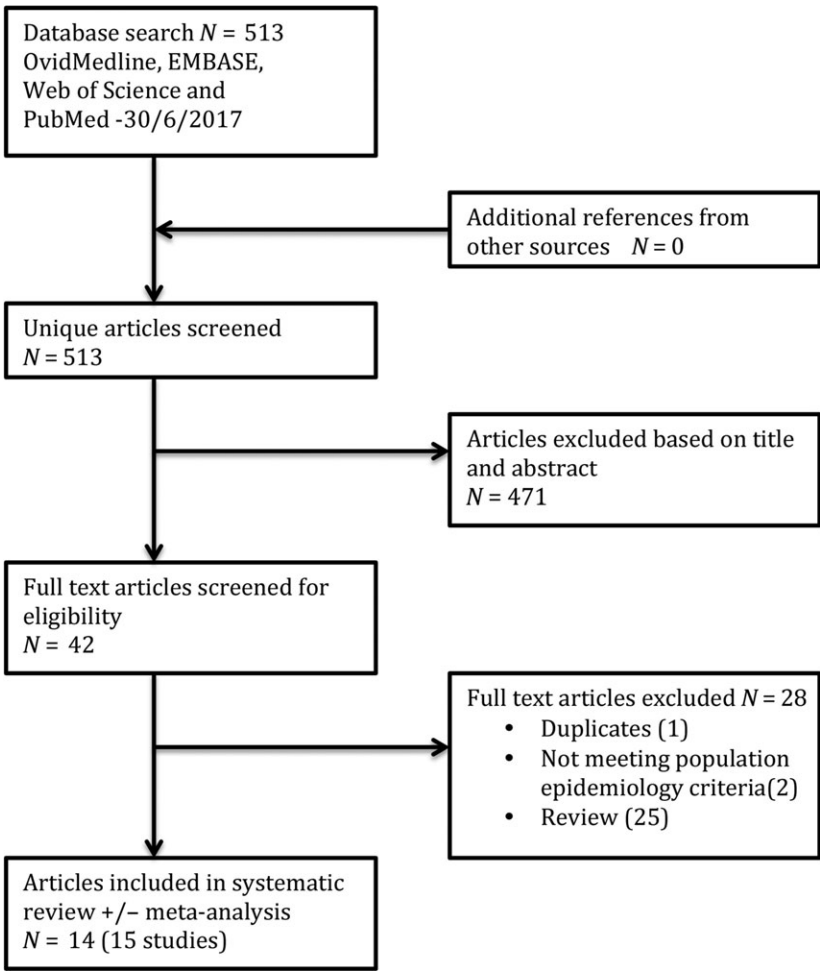

Figure 1 Flow diagram of the literature search.

obesity, suggesting that IIH is a public health issue, which may be amenable to population-targeted prevention. Females between the ages of 14 and 45 years had a particularly high incidence of IIH, especially in countries where the overall incidence of IIH was high. There was no association between incidence rate of IIH and year of study despite the recognition that obesity prevalence is increasing [4]. The obesity pandemic has been positively associated with increasing disease burden of IIH. Treatments for IIH include weight reduction [30], acetazolamide [31] and shunting procedures including the less well-established procedure of transverse sinus stenting [32]. However, the condition exerts a considerable long-term economic [33] and clinical burden [34] with quality of life impairment comparable to that in patients with multiple sclerosis and a history of optic neuritis [35]. One previous study has also shown that the increase in IIH incidence mirrors increasing population obesity [8], emphasizing the need for targeting obesity prevention.

Compounding a lack of public health familiarity with IIH is the poorly recorded prevalence of IIH, which hides the burden of chronic ill health from IIH [36]. The measurement of STROND criteria has shown that the quality of population-based epidemiological studies in IIH to date is suboptimal. A lag period from increasing adolescent and adult obesity to identification of IIH and relatively small incidence rates may have obscured the public recognition of this complication of obesity. Our systematic review highlights the need for accurate longitudinal measurements in IIH epidemiology to determine the effectiveness of public health measures for prevention.

Strengths and limitations

The pooled incidence figure of IIH had a very high heterogeneity with I^2 98%. Possible explanations may be variations in how incidence was calculated. Some studies estimated the population attending hospital as the denominator, whereas other studies used population sizes from census samples. Also, there was variation in whether estimates were calculated using the

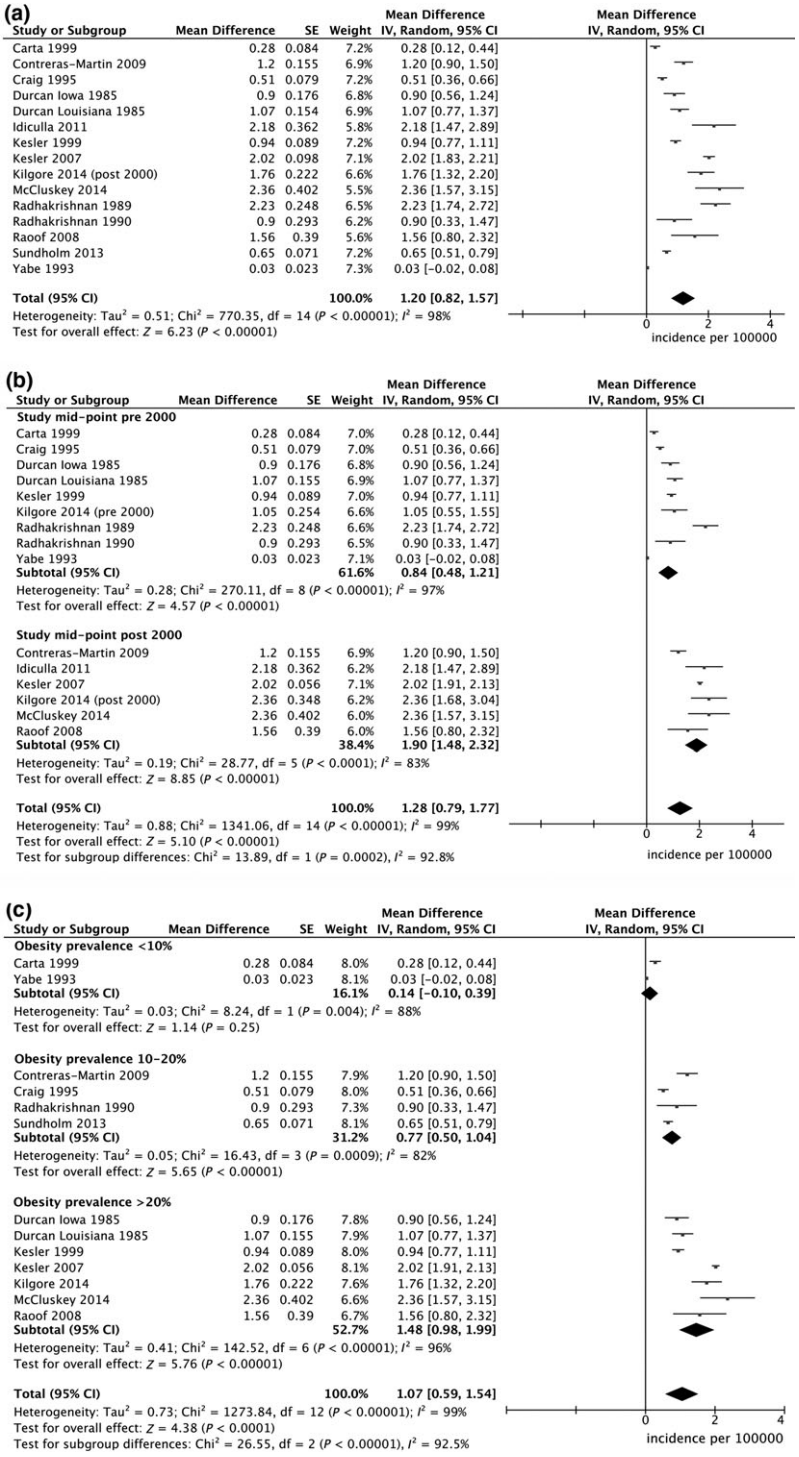

Figure 2 (a) Incidence studies of idiopathic intracranial hypertension. (b) Incidence studies of idiopathic intracranial hypertension stratified for year of study up to 2000 and from 2000 onwards. (c) Incidence studies of idiopathic intracranial hypertension stratified for national obesity prevalence records.

whole population or only those above a certain age (e.g. 16 and over). Some studies did not describe how incidence was calculated. There was also wide variation in the methods used for identifying all cases such as contacting local neurologists or using computer-based record systems. Few studies employed overlapping methods of ascertainment, although ascertainment methodology appears to have improved in more recent studies. In addition, the funnel plot lacked symmetry, which could be due to a number of reasons including publication bias (such as a lack of smaller studies showing lower incidence rates) or

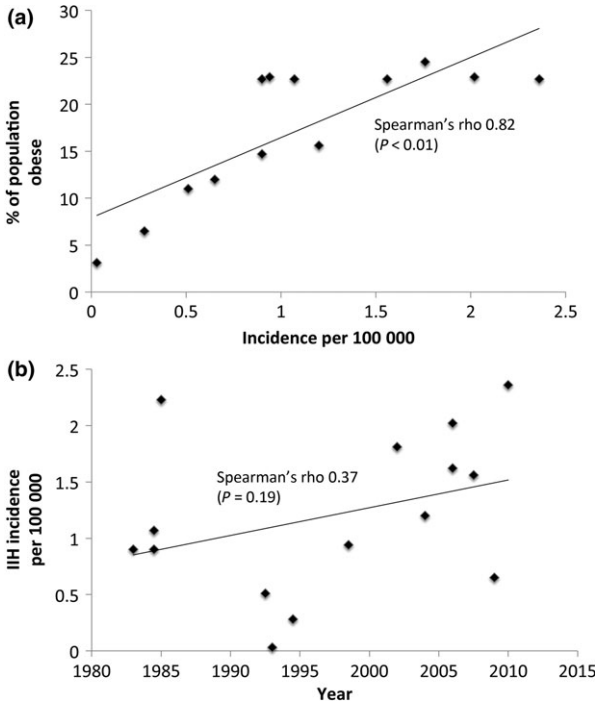

Figure 3 (a) Incidence studies of idiopathic intracranial hypertension and national obesity prevalence. (b) Incidence studies of idiopathic intracranial hypertension and midpoint year of study.

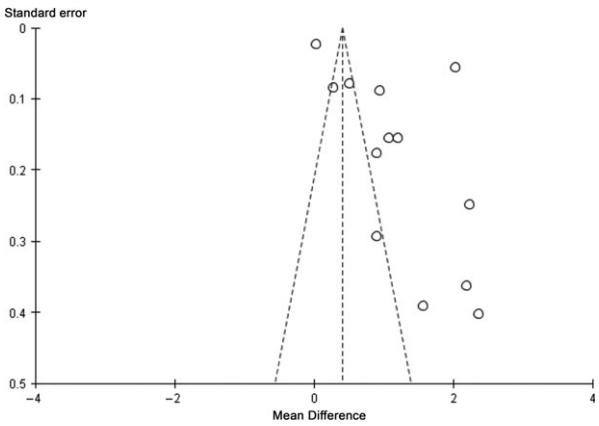

Figure 4 Funnel plot of incidence studies of idiopathic intracranial hypertension.

study heterogeneity. The pooled incidence rate of IIH may therefore not be reliable as a global estimate of IIH incidence, whereas the association between IIH incidence and country-specific obesity prevalence is an important finding worthy of further public health study.

This systematic review was restricted to adults (14 years and older). Some clinicians consider childhood IIH as a different entity, which merits similar review [5].

Justification of exclusion

As ophthalmoscopic errors are common amongst obese people with headaches, overdiagnosis of IIH can occur resulting in inaccurate clinical diagnosis and unreliable epidemiological data for IIH. In our study, recognized criteria for IIH were applied to ensure an elevated cerebrospinal fluid pressure was documented and so to avoid inaccurate diagnosis. Each of the studies clearly documented the use of appropriate diagnostic criteria for IIH.

Assessment of quality of included studies

There were no exclusion criteria for epidemiological studies in appropriately defined IIH as a comprehensive assessment of the quality of population-based epidemiological studies in IIH was planned. The STROND criteria are a relatively new development in methodological assessment and, to our knowledge, have not yet been used as a template for measuring the quality of neuroepidemiological studies [1]. Most of the IIH epidemiological studies in our review predated these criteria. However, application of the STROND criteria to selected population-based epidemiological studies of IIH has highlighted the need for improved quality of neuroepidemiological studies in IIH. The STROND criteria were not devised for retrospective quality assessment but rather to help future studies inform health policy research. However, our study has provided some pointers to improve the reporting of IIH epidemiology, including measuring prevalence, calculating confidence intervals, measuring disease burden disability, recording types of IIH (particularly recording fulminant IIH) and providing rates of hospital admission.

Future studies

Our study prompts the need for large, longitudinal quality-assured registers or studies to systematically and objectively identify active IIH, so that the natural history and prevalence of IIH can be accurately reported. Accurate prevalence data (with evidence of raised intracranial pressure fulfilling the revised and updated modified Friedman criteria [12]), including objective and systematic measurement of outcome, should be a goal of both public health neurology and multidisciplinary specialist clinics. As there is increasing evidence that public health interventions demonstrate cost-effective health benefits [37], this work suggests that population-based epidemiological studies of IIH offer an outcome measure from public health interventions especially if targeted at younger people.

Table 2 Strengths, weaknesses and STROND scores for population-based studies in idiopathic intracranial hypertension

Author/year(s) of study	Country	Criteria	Strengths (size of study, ascertainment)	Weaknesses (size of study, ascertainment)	Basic requirements $N = 29$	All requirements $N = 43$
Durcan [17]/1984–1985	Iowa, USA	MD		Small. Relied on physician response	23	26
Durcan [17]/1984–1985	Louisiana, USA	MD		Small. Relied on physician response	19	18
Radhakrishnan [16]/1982–1989	Libya	MD		Hospital specialty clinics	23	28
Radhakrishnan [18]1976–1990	USA	MD	Medical record linkage	Very small study	23	28
Yabe [19]/1993	Japan	MD		Very small study. Hospital records	14	16
Craig [20]/1991–1995	Northern Ireland	MD		Small study. Regional hospital database	18	25
Kesler [22]/1998–1999	Israel	MD	Large study	Specialist invitation for recruitment. Unavailable data from 2 hospitals	22	27
Carta [21]/1990–1999	Italy	MD		Very small study. Hospital computer	21	25
Kesler [24]/2005–2007	Israel	MD	Large study	Computerized medical record	21	27
Raoof [23]/2007–2008	England	F 2002		Very small. Regional hospital database	21	28
Contreras- Martin [25]/1999–2009	Spain	MD	Large study	Tertiary neurology hospital search	16	20
Idiculla [26]/2001–2011	Oman	MD		Small study. Regional hospital	18	19
McCluskey [6]/2007–2014	Northern Ireland	MD	Multiple hospital sources	Small study	26	33
Sundholm [27]/2006–2013	Sweden	MD	Large study. Validated national register		23	28
Kilgore [8]/1990–2014	Olmsted County, USA	MD	Large study. Multicentre medical record database		25	35
Median score (range)					21 (14–26)	26.5 (16–35)

MD, modified Dandy criteria; F, Friedman criteria 2002. Study weaknesses: size of study very small $N \leq 10$; small $N \leq 50$. Study strengths: multiple sources of ascertainment.

Clinical experience suggests that most IIH patients have a monophasic illness but a substantial minority of patients remain symptomatic, often without documentation of persistently elevated intracranial pressure [36]. Patients who have been diagnosed with IIH and who have persistently elevated intracranial pressure should be managed (and recorded) differently from patients with persistent headache and neuropsychiatric symptoms without elevated intracranial pressure in the absence of progressive visual deficits.

There has been an increase in global age-standardized BMI between 1974 and 2014 [2]. The rate of increase in childhood and adolescent obesity is exceeding the rate of increase in adult obesity in many countries [4]. Some studies have shown an inverse association between obesity levels and participation in exercise especially amongst girls [38]. There is emerging evidence, however, that early school-based interventions combined with diet and physical activity components can prevent obesity in the young, but any regulatory measures may have to overcome undermining 'complexity' tactics from the food industry [39]. Future study of the impact of decreasing obesity prevalence and IIH incidence is required to strengthen a causality claim.

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Disclosure of conflicts of interest

The authors declare no financial or other conflict of interests.

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