Reference Values For Intracranial Pressure And Lumbar Cerebrospinal Fluid Pressure: A Systematic Review

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Research

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Abstract

Background

Although widely used in the evaluation of the diseased, normal intracranial pressure and lumbar cerebrospinal fluid pressure remains sparsely documented. Intracranial pressure is different from lumbar cerebrospinal fluid pressure. In addition, intracranial pressure differs considerably according to body position of the patient. Despite this, the current reference interval are used indistinguishable for intracranial and lumbar cerebrospinal fluid pressure, and body position dependent reference intervals does not exist. In this study, we aim to establish these reference intervals.

Method

A systematic search was conducted in MEDLINE, EMBASE, CENTRAL, and Web of Sciences. Methodological quality was assessed using an amended version of the Joanna Briggs Quality Appraisal Checklist. Intracranial pressure and lumbar cerebrospinal fluid pressure were independently evaluated and subdivided into body positions. Quantitative data were presented with mean ± SD, and 90% reference intervals.

Results

Thirty-six studies were included. Nine studies reported values for intracranial pressure, while 27 reported values for the lumbar cerebrospinal fluid pressure. Reference values for intracranial pressure were -5.9 to 8.3 mmHg in the upright position and 0.9 to 16.3 mmHg in supine position. Reference values for lumbar cerebrospinal fluid pressure were 7.2 to 16.8 mmHg and 5.7 to 15.5 mmHg in the lateral recumbent position and supine position, respectively.

Conclusions

This systematic review is the first to provide position-dependent reference values for intracranial pressure and lumbar cerebrospinal fluid pressure. Clinically applicable reference values for normal lumbar cerebrospinal fluid pressure was established, and were in accordance with previously used reference values. For intracranial pressure, this study strongly emphasizes the scarce normal material, and highlights the need for further research on the matter.

Background

Measurement and analysis of intracranial pressure (ICP) are used to inform treatments and management of numerous neurosurgical diseases, e.g., traumatic brain injury, acute intracranial hemorrhages, idiopathic intracranial hypertension, and hydrocephalus[1–4]. However, values for normal ICP measured intracranially remain sparsely documented, and the currently used reference interval (7 to 15 mmHg[5]) are based on studies in which lumbar cerebrospinal fluid opening pressure (LCSF$_{op}$) is used as a surrogate parameter for ICP or extrapolated from patients with a suspected ICP disorder[5–11].
In the 1920s and 30s, it was assumed that ICP measured intracranially was equal to LCSF$_{op}$ measured at a lumbar spine level[12, 13]. This has, in recent years, been subject to much debate [14–18], and where some studies have documented similar values for intracranial measurements and lumbar measurements[14, 16], others find considerable differences between the two measurement-sites[15, 17, 18]. The comparison of these studies is hampered by differences in study design, particularly dissimilarities in body position during the measurement and included study participants[14–17, 19, 20].

It is well known that body position alters ICP[9, 19–22], e.g., ICP decrease in vertical position compared to horizontal position[9, 20, 22], and increase significantly with the body placed in lateral recumbent position compared to supine position[19, 23–25]. Based on this, it is highly likely that different reference intervals for ICP should be established for different body positions.

In this systematic review, we aim to 1) determine reference intervals for normal ICP and LCSF$_{op}$, and 2) examine if reference intervals for ICP depend on measurement-site and body position.

**Methods**

Prior to initiating this systematic review, the protocol was registered at PROSPERO (October 30, 2019, identification code: CRD42019143018). The review has been conducted in accordance with the PRISMA guidelines, and a completed PRISMA checklist is available in Appendix 1.

**Eligibility criteria**

All included studies had to provide 1) measurements conducted in humans, 2) original values for either ICP or LCSF$_{op}$, and 3) ICP measured either intracranially (parenchymal, intraventricular, epidural, subdural, or subarachnoid) or LCSF$_{op}$ measured during a lumbar puncture. All age-groups were included.

Patients with intracranial pathology that potentially could alter ICP dynamics (e.g., hydrocephalus, idiopathic intracranial hypertension, intracranial hemorrhage, arteriovenous malformation, intracranial tumor, intracranial abscesses or other significant space-occupying processes within the brain) were excluded.

**Data search**

On July 16st 2019, we conducted a search in MEDLINE Ovid (1946 to July 2019), Embase Ovid (1974 to July 2019), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library and Science Citation Index Expandex (1900 to July 2019), and Conference Proceeding Citation Index – Science (Web of Science) (1990 to July 2019). There was no restriction on the publication period. We included all peer-reviewed published studies without consideration for publication status or study design. The search was conducted in English, and studies with a non-English title or abstract were thus excluded. Non-English manuscripts, with an English title and abstract, were translated by a native speaker. The search strategy is attached in Appendix 2.
If published data in the included studies were insufficient, the authors were contacted in order to retrieve raw data. The systematic search was supplemented by a manual reference-search of included studies. Finally, an expert in the field (MJ) was asked to identify any obviously missing studies.

**Study selection and data extraction**

Four investigators (CSR, MHO, NHN, SHP) reviewed the studies for eligibility. Each study was assessed by two different investigators for the title, abstract and full-text screening. Discrepancies were initially resolved between the four investigators, and if this was not possible, an expert (MJ) had the deciding vote. The screening was conducted via Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Study design, demographics, and information regarding ICP-monitoring were extracted from each study.

Study data were extracted from Covidence by NHN and verified by MHO. Disagreements were resolved by discussion.

**Quality assessment**

The methodological study quality was independently assessed by two investigators (MHO, NHN). No intervention-based studies were included, and thus, traditional assessment methods for systematic reviews could not be used. Instead, a quality assessment method was created inspired by the Joanna Briggs Institute Critical Appraisal Tool[26]. Two parts of the tool were, however, irrelevant in the assessment of study type and therefore replaced; 1) “Was the exposure measured in a valid and reliable way?” was replaced with “Was the measurement method described in details?” and 2) “Were the outcomes measured in a valid and reliable way?” was replaced with “Was the included population without current or previous intracranial pathology that could alter ICP dynamics?”

**Data synthesis**

All statistical analyses were performed in RStudio (R 3.6.2, R Development Core Team (2019), Vienna, Austria). Since all included studies were observational, and the primary purpose of this review was to determine a reference interval for ICP, a conventional meta-analysis was not applicable.

Instead, included studies were pooled into two groups, 1) studies in which ICP was measured, and 2) studies in which LCSF_{op} was measured.

Raw data were assessed for normality and presented as mean ± standard deviation (SD), 95% confidence intervals (CI) and with coherent reference intervals (defined as 5th to 95th percentile)[5]. If statistical values other than SD were presented (e.g., 95% confidence intervals or reference intervals), SD was manually calculated based on the given statistical data according to the Cochrane Handbook of Systematic Reviews[27]. For studies where only the median and interquartile range (IQR) were presented, the median was directly transformed to a mean, while SD was estimated from IQR by SD = IQR/1.35, as recommended in the Cochrane Handbook of Systematic Reviews[27]. Finally, if pressure values were reported in other units (e.g., mmH$_2$O or cmH$_2$O) it was converted to mmHg.
Normal ICP and LCSF$_{op}$ were subdivided into different body positions stratified by study and presented in a forest plot, including mean values and 95% CI. The corresponding weighted reference intervals for the different body positions were subsequently presented in a table for ICP and LCSF$_{op}$. Reference intervals are presented in both mmHg and cmH$_2$O.

The different body positions were compared using a two-tailed Students t-test, and P-values were presented after Bonferroni correction. P-values < 0.05 were considered significant. The included studies provided insufficient data to perform a meaningful multivariate analysis adjusting for age, gender, monitoring equipment, neck position, and zeropoint for ICP measurement-site.

**Results**

The search strategy identified a total of 2,515 studies. After the removal of duplicates, 1,790 studies remained. The abstract and title screening left 126 studies, and based on full-text screening, 44 studies were included (Fig. 1). Study characteristics are presented in Table 1.
Table 1
Characteristics of included studies

| Study            | Type of study               | Type of population | Measurement place | No. of participant | Mean age or range | Included in analysis* |
|------------------|----------------------------|--------------------|-------------------|--------------------|-------------------|-----------------------|
| Albeck 1991      | Prospective, observational | Healthy            | Lumbar            | 8                  | 22–28             | Yes                   |
| Albeck 1998      | Prospective, observational | Healthy            | Lumbar            | 52                 | 60                | Yes                   |
| Andresen 2014    | Prospective, observational | Pseudo-healthy     | Parenchymal       | 4                  | 67                | Yes                   |
| Avery 2010       | Prospective, observational | Pseudo-healthy     | Lumbar            | 197                | 1–18              | Yes                   |
| Avery 2014       | Case report, literature review | Pseudo-healthy     | Lumbar            | 1                  | 12                | Yes                   |
| Beck 2017        | Prospective, observational | Pseudo-healthy     | Lumbar            | 17                 | -                 | Yes                   |
| Blomquist 1986   | Prospective, observational | Pseudo-healthy     | Lumbar            | 18                 | 0–15              | Yes                   |
| Bono 2003        | Prospective, observational | Pseudo-healthy     | Lumbar            | 111                | 40                | Yes                   |
| Bø 2010          | Prospective, observational | Pseudo-healthy     | Lumbar            | 348                | 47                | Yes                   |
| Chiari 2017      | Retrospective, observational | Pseudo-healthy     | Parenchymal       | 41                 | 43                | Yes                   |
| Chapman 1990     | Prospective, observational | Pseudo-healthy     | Ventricular       | 5                  | 28                | Yes                   |
| Corbett 1983     | Prospective, observational | Healthy            | Lumbar            | 15                 | -                 | Yes                   |
| Eklund 2016      | Prospective, observational | Healthy            | Lumbar            | 11                 | 46                | Yes                   |
| Ekstedt 1978     | Prospective, observational | Pseudo-healthy     | Lumbar            | 100                | -                 | Yes                   |

* Studies were not included in the analysis, if they provided insufficient statistical data to calculate a mean and standard deviation
| Study           | Type of study       | Type of population | Measurement place | No. of participant | Mean age or range | Included in analysis* |
|-----------------|---------------------|--------------------|-------------------|-------------------|-------------------|-----------------------|
| Ellis 1994      | Prospective, observational | Pseudo-healthy    | Lumbar            | 33                | 8                 | Yes                   |
| Fleischman 2012 | Retrospective, observational | Pseudo-healthy    | Lumbar            | 12118             | 54                | Yes                   |
| Friden 1983     | Retrospective, observational | Pseudo-healthy    | Lumbar            | 150               | -                 | Yes                   |
| Gilland 1969    | Retrospective, observational | Healthy          | Lumbar            | 15                | 25                | Yes                   |
| Gilland 1974    | Prospective, observational | Healthy          | Lumbar            | 31                | 23                | Yes                   |
| Gonzalez 2017   | Prospective, case-control | Pseudo-healthy    | Lumbar            | 28                | 41                | No                    |
| Hannerz 1995    | Prospective, observational | Healthy          | Lumbar            | 19                | 52                | Yes                   |
| Kaiser 1986     | Prospective, observational | Pseudo-healthy    | Lumbar            | 49                | 30 (24–41) weeks | Yes                   |
| Kawasaki 1998   | Retrospective, case-control | Pseudo-healthy    | Lumbar            | 1                 | 51                | Yes                   |
| Lakke 1968      | Prospective, observational | Healthy          | Lumbar            | 34                | -                 | No                    |
| Langvatn 2019   | Retrospective, observational | Pseudo-healthy    | Parenchymal       | 12                | 3                 | Yes                   |
| Lawley 2017     | Prospective, observational | Pseudo-healthy    | Ventricular       | 8                 | 35                | Yes                   |
| Lee 2011        | Retrospective, observational | Pseudo-healthy    | Lumbar            | 44                | 9                 | Yes                   |
| Lundberg 1960   | Prospective, case-control | Pseudo-healthy    | Ventricular       | 1                 | 45                | No                    |
| Magneli 2016    | Prospective, case-control | Pseudo-healthy    | Parenchymal       | 1                 | 8                 | Yes                   |

* Studies were not included in the analysis, if they provided insufficient statistical data to calculate a mean and standard deviation
| Type of study   | Type of population | Measurement place | No. of participant | Mean age or range | Included in analysis* |
|----------------|--------------------|-------------------|--------------------|-------------------|-----------------------|
| Mahr 2016⁷⁸    | Prospective, observational | Pseudo-healthy   | 35                 | 73                | No                    |
| Malm 2011⁵     | Prospective, observational | Healthy       | 40                 | 70                | Yes                   |
| Martin 1978⁷⁹  | Prospective, case-control | Pseudo-healthy   | 1                  | 19                | No                    |
| Pedersen 2018⁴¹ | Retrospective, observational | Pseudo-healthy   | 35                 | 4–85              | Yes                   |
| Petersen 2016⁵⁵ | Prospective, observational | Pseudo-healthy   | 11                 | 44                | Yes                   |
| Puhringer 1997³⁷ | Prospective, observational | Healthy       | 5                  | 25–38             | Yes                   |
| Purvin 2000⁵²  | Retrospective, case-control | Pseudo-healthy   | -                  | -                 | No                    |
| Riedel 2020    | Prospective, observational | Pseudo-healthy   | 44                 | 60                | Yes                   |
| Schwartz 2013⁵⁸ | Prospective, observational | Pseudo-healthy   | 55                 | 56                | Yes                   |
| Shapiro 1980²⁹ | Prospective, observational | Healthy       | 23                 | 0–55              | Yes                   |
| Skau 2013³⁰    | Prospective, case-control | Healthy       | 20                 | -                 | Yes                   |
| Skipper 2019³¹ | Retrospective, case-control | Healthy       | 24                 | 33                | No                    |
| Sugita 1985⁶⁴  | Prospective, case-control | Pseudo-healthy   | 3                  | 38                | No                    |
| Whiteley 2006¹¹ | Retrospective, observational | Pseudo-healthy   | 242                | -                 | Yes                   |
| Wibroe 2016⁶⁵  | Prospective, observational | Pseudo-healthy   | 28                 | 37                | Yes                   |

* Studies were not included in the analysis, if they provided insufficient statistical data to calculate a mean and standard deviation
The majority of studies reported a mean value with coherent SD or a mean value with either 95% CI or reference intervals, from which SD could be calculated (n = 32). In a few studies, only median and IQR were reported (n = 4). Studies that only reported a range or a mean, and where no further statistical data could be provided from the authors were omitted from analysis (n = 8). Thus, 36 studies remained in the data analysis.

**Reference intervals for ICP and LCSF<sub>op</sub>**

Reference intervals differed significantly between body positions (e.g., lateral recumbent position LCSF<sub>op</sub> versus supine LCSF<sub>op</sub> (P = 0.04), and upright ICP versus supine ICP (P < 0.01)). Details are shown in Table 2 for both ICP and LCSF<sub>op</sub>.

| ICP       | No. of studies | No. of participants | Mean (reference interval) [mmHg] | Mean (reference interval) [cmH<sub>2</sub>O] |
|-----------|----------------|---------------------|---------------------------------|---------------------------------------------|
| supine    | 6              | 62                  | 8.6 (0.9–16.3)                  | 11.7 (1.2–22.2)                            |
| upright   | 6              | 62                  | 1.0 (-5.9–8.3)                  | 1.3 (-8.7–11.2)                            |
| daytime   | 2              | 45                  | -0.1 (-12.0–12.2)               | -0.15 (-16.3–16.6)                         |
| nighttime | 3              | 57                  | 6.3 (-15.8–28.2)                | 8.6 (-21.5–38.3)                           |

| CSF<sub>op</sub> | No. of studies | No. of participants | Mean (reference interval) [mmHg] | Mean (reference interval) [cmH<sub>2</sub>O] |
|------------------|----------------|---------------------|---------------------------------|---------------------------------------------|
| supine           | 7              | 389                 | 10.7 (5.7–15.5)                 | 14.4 (7.5–21.1)                            |
| lateral recumbent| 21             | 13,359              | 11.9 (7.2–16.8)                 | 16.3 (9.8–22.8)                            |

Nine studies provided values for ICP measured intracranially. Reference intervals were subdivided into four groups based on body position: 1) supine position with a mean ICP of 8.6 mmHg (SD 4.7, reference interval 0.9 to 16.3 mmHg), 2) upright position with a mean ICP of 1.0 mmHg (SD 4.3, reference interval -5.9 to 8.3 mmHg), 3) continuous daytime measurement with a mean ICP of -0.1 mmHg (SD 7.4, reference interval -12.0 to 12.2 mmHg), and 4) continuous nighttime measurement with a mean ICP of 6.3 mmHg (SD 13.3, reference interval -15.8 to 28.2) (Fig. 2, Table 2).

Twenty-seven studies provided values for LCSF<sub>op</sub> measured by lumbar puncture. LCSF<sub>op</sub> was subdivided into two groups: 1) the supine position with a mean LCSF<sub>op</sub> of 10.7 mmHg (SD 3.0, reference interval 5.7 to 15.5 mmHg), and 2) the lateral recumbent position with a mean LCSF<sub>op</sub> of 11.9 mmHg (SD 2.9,
reference interval 7.2 to 16.8 mmHg) (Fig. 2, Table 2). There was a statistical difference between ICP values in the supine position and LCSF$_{op}$ values in the supine position ($P = 0.03$).

There was no statistical difference between reference intervals for LCSF$_{op}$ based solely on the healthy population compared to reference intervals for LCSF$_{op}$ based solely on the pseudo-healthy population. The difference between healthy individuals and pseudo-healthy individuals in lateral recumbent position was 1.4 mmHg ($P = 0.34$), and in supine position 1.0 mmHg ($P = 0.73$).

**Quality of included studies**

The overall methodological quality of the study designs was moderate. Out of seven, the average score of the included studies was 4.5.

None of the studies in which ICP was measured were based on completely healthy individuals, and in only two studies, the primary aim was to determine reference intervals for ICP. For the studies in which ICP was measured, the overall methodological study quality was moderate (average study quality = 4/7).

In the group of LCSF$_{op}$, the overall study quality was generally higher (average study quality = 5/7) and a few studies included completely healthy individuals ($n = 13$) [5, 6, 34–36, 7, 24, 28–33]. In general, studies with LCSF$_{op}$ consisted of a significantly higher number of study participants (Table 1).

**Discussion**

This systematic review aimed to establish reference intervals for normal ICP and LCSF$_{op}$. Through an extensive literature search, 44 studies examining either ICP or LCSF$_{op}$ in pseudo-normal or normal participants were identified, and of these, 36 provided sufficient pressure values and statistical data to calculate reference intervals. Nine studies reported ICP values, while 27 reported LCSF$_{op}$ values. The overall study quality was moderate. For ICP, the study material were scarce, and the reference intervals were based on a small sample size. Data on LCSF$_{op}$ were, in comparison, comprehensive in both lateral recumbent position and supine position. Finally, the reference intervals for both ICP and LCSF$_{op}$ were found to differ significantly between body positions, demonstrating the need for position-dependent reference intervals.

The literature further indicates that age, weight, neck position, zeropoint for measurement-site, and monitoring equipment is of great importance in measurement of ICP and LCSF$_{op}$ [10, 24, 37–42]. Especially zeropoint is of uttermost importance when measuring ICP in upright position. In supine and lateral recumbent position, zeropoint matters to the extend that it has to be in the midline of the patient which is a clinical standard in most neurological and neurosurgical departments. However, only nine of the included studies described the zeropoint of measurements. In terms of the studies reporting on measurement in upright position two out of six studies reported on zeropoint. Thus, for the purpose in
this systematic review, data in the included studies were too scarcely reported for meaningful analysis, and thus the reference values were not corrected for the above mentioned factors.

The measured intracranial pressure is clearly dependent on the zero point of the measurements. In supine and lateral recumbent position, it is less important as long as it is in the midline of the patient. However, in Nine of the study reported on zero point,

**Reference intervals for ICP**

Due to the still invasive nature of obtaining ICP, it is ethically unacceptable to examine ICP in healthy normal individuals. Several non-invasive ICP measuring methods have been developed, and though they can be useful to estimate interpatient ICP differences, e.g., during follow-up, none are currently accurate enough to measure ICP values[43, 44].

The studies in this review included pseudo-normal patients[21, 45–47], and we identified no published studies of ICP on completely healthy participants. In the last decade, a new telemetric monitoring technique has become available, allowing for ICP measurements for several months after implantation[48–50]. This has resulted in ICP measurements in groups outside of the traditional patient-categories with suspected ICP disorders. Andresen et al. implanted a telemetric ICP monitor in patients who had a small demarcated intracranial tumor surgically removed, thus establishing a pseudo-normal cohort[45]. Though this cohort is not completely healthy, long-term measurements via the telemetric ICP monitor provide ICP values at a time when intracranial conditions, including ICP, can be considered normal. This is an improvement to previous research, which have been mainly based on patients undergoing diagnostic evaluation for a suspected ICP disorder[21, 39, 51, 52]. Future research to establish normal ICP, until quantitative non-invasive technology is developed, could benefit from this telemetric monitoring technique and, hopefully, expand the material on ICP values obtained in pseudo-normal humans.

In this review, we found a reference interval for ICP in the supine position from 0.9 to 16.3 mmHg, based on six studies with a total of 62 participants[21, 45, 51, 53–55]. The reference intervals are based on a small sample size and differ substantially in their findings of normal ICP, and do, therefore, not represent a clinically applicable reference interval.

Since most humans, and in terms of patients specifically idiopathic intracranial hypertension and normal pressure hydrocephalus patients, spend the majority of their lives in the upright (vertical) position, a reference interval for this specific position is needed for interpreting diagnostic long-term ICP monitoring. Based on six studies with a total of 62 participants[21, 39, 45, 53–55], this review found a reference intervals for ICP in the upright position from −6.2 to 8.0 mmHg. Though too wide to serve as a clinically applicable reference interval, the data show that negative ICP values can be normal in an upright position[45, 56].
For daytime ICP, the established reference intervals were likewise based on a limited number of studies (n = 2) and study participants (n = 45)[42, 57]. Furthermore, there are large interpersonal differences in the amount of time spend in an upright position during the day. These factors proberly result in the wide reference interval from − 12.0 to 12.2 mmHg. As with the reference interval for ICP in the upright position, this does not serve as a practical tool in clinical decision making.

For nighttime, we were able to establish a reference interval from − 15.8 to 28.2 mmHg. Besides a limited number of studies (n = 3) and participants (n = 57) addressing the matter[42, 57, 58], body position during sleep may vary considerably among patients. Furthermore, the degree of sleep apnoe has also been found to highly impact ICP[42]. Combined, this could potentially cause significant variations in measured ICP and, result in the very wide and clinical unuseful reference interval. Unfortunately, the included studies did not provide information on body position nor sleep apnoe coherent to ICP values.

Reference intervals for LCSF_{op}

The majority of included studies on LCSF_{op} (81%) performed pressure measurement in a lateral recumbent position[6, 7, 34–36, 41, 59–64, 8, 65–70, 10, 23, 29–33], thus establishing a reference interval in this position from 7.2 to 16.8 mmHg. There were no significant difference between the reference intervals in healthy individuals versus pseudo-healthy individuals. The establish reference interval is similar to the reference of 7 to 15 mmHg routinely used in clinical practice[5, 18, 23, 24, 45].

Seven studies obtained LCSF_{op} values in supine position[5, 8, 24, 28, 59, 71, 72], resulting in a reference interval from 5.7 to 15.5 mmHg. Participants in three out of the seven studies were completely healthy[5, 24, 28]. There was no significant difference between reference intervals in healthy individuals versus pseudo-healthy individuals.

When comparing supine LCSF_{op} to supine ICP, we found a difference between the means corresponding to 2.1 mmHg (P = 0.03). These results suggest that supine LCSF_{op} is not optimal as a surrogate marker of supine ICP. To our knowledge, there are no studies that comparing simultaneously measured supine ICP with supine LCSF_{op}.

Posture-dependent pressure differences

Postural-dependent pressure changes have mainly been evaluated in studies investigating ICP[19, 54]. Andresen et al. compared lumbar recumbent position to supine position in 31 patients with intracranial ICP monitoring and found that ICP increased approximately 5 mmHg in the lateral recumbent position, thus a significantly higher difference than found between LCSF_{op} in recumbent position versus supine position in this review[19]. This postural-related difference in ICP may be caused by spine flexion and, in particular, flexion of the neck during lateral recumbent position in the study by Andresen et al[19]. A flexed neck could theoretically compress the jugular veins, thus hindering the venous return to the heart from the
head, thereby increasing ICP\cite{40, 73–75}. Many studies have emphasized the importance of a neutral neck during the measurement of LCSF\textsubscript{op}\cite{23, 24, 40, 73}.

Though statistically significant, the mean LCSF\textsubscript{op} difference of 1.2 mmHg between the lateral recumbent position and supine position hardly has any clinical implications (Fig. 2). This relatively small difference might be explained by LCSF\textsubscript{op} in the lateral recumbent position having been measured with the neck in a neutral position. Unfortunately, the significant change in LCSF\textsubscript{op} caused by neck position alone has not previously been subject to much debate. Thus, only six of the included studies examining LCSF\textsubscript{op} documented that LCSF\textsubscript{op} was obtained simultaneously with a neutral neck position\cite{6, 24, 29, 32, 35, 68}. To establish an accurate reference interval of LCSF\textsubscript{op}, the neck should be held in a neutral position during all LCSF\textsubscript{op} measurements.

**Conclusions**

In this systematic review, we aimed to establish reference intervals for ICP and LCSF\textsubscript{op}.

The data on ICP was not sufficient to establish clinically applicable reference intervals for either supine position, upright position, daytime, or nighttime. Negative ICP in upright position do however seem to be normal. For LCSF\textsubscript{op} we estimated clinically applicable reference intervals in both lateral recumbent position (6.3 to 15.9 mmHg) and supine position (5.3 to 15.1 mmHg). This systematic review highlights the need for future research within the field of reference intervals for ICP.

**Declarations**

**Ethics appraisal and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and material**

The dataset used and analysed during the current study are available from the corresponding author on reasonable request.

**Competing interest**

The authors declare that they have no competing interests.

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**Authors’ contributions**

NHN MHO, SSP, CSR, MJ designed the study.

NHN, MHO, SSP, CSR screened and extracted data from studies.

NHN and MHO drafted the manuscript.

All authors reviewed the manuscript.

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Not applicable.

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Figures

Figure 1

Flowchart of study selection process The section “insufficient data” covers that these studies did not report sufficient statistical data to be included in statistical analysis. Thus, no standard deviations,
confidence intervals or reference intervals were reported in these studies. The included articles “Other sources” were found by manual searching the reference list of included studies.

**Figure 2**

Forest plot of lumbar cerebrospinal fluid pressure and intracranial pressure Two forest plots describing the weighed average of lumbar cerebrospinal fluid pressure (LCSFop) and intracranial pressure (ICP) reported in each included study. The LCSFop is presented to the left, and grouped into different body positions: lateral recumbent position and supine position. ICP is presented to the right, and also subgrouped into different body positions: daytime, nighttime, supine and upright position.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1PRISMAchecklist.doc
- Appendix2Searchstrategy.docx
- Appendix3QualityAssessment.docx