Am J Transl Res 2025;17(2):1437-1447
www.ajtr.org /ISSN:1943-8141/AJTR0160594

*Original Article*

# Efficacy and safety of idiopathic normal pressure hydrocephalus shunting: a systematic review and meta-analysis

Xiaowei Liu[1,2,3,4,5*], Bei Pan[2,3,4*], Xiyuan Deng[1,2,3,4], Keyu Chen[5], Xin Liu[6], Yongxiu Yang[1], Kehu Yang[2,3,4]

*[1]The First School of Clinical Medicine, Lanzhou University, Lanzhou, Gansu, China; [2]Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu, China; [3]Key Laboratory of Evidence Based Medicine and Knowledge Translation of Gansu Province, Lanzhou, Gansu, China; [4]Evidence-Based Social Science Research Center, School of Public Health, Lanzhou University, Lanzhou, Gansu, China; [5]Department of Neurosurgery, Chengdu Second People's Hospital, Chengdu, Sichuan, China; [6]Department of Orthopedics, Chengdu Second People's Hospital, Chengdu, Sichuan, China. [*]Equal contributors.*

Received September 17, 2024; Accepted January 22, 2025; Epub February 15, 2025; Published February 28, 2025

**Abstract:** Objective: Shunting is commonly used in patients with idiopathic normal pressure hydrocephalus (iNPH). However, evidence comparing the relative effectiveness and safety of different iNPH shunting methods is lacking. Therefore, this systematic review investigated the efficacy and safety of different iNPH shunts. Methods: The PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science databases were systematically searched for articles comparing iNPH shunting from inception to July 29th, 2023 to identify randomized controlled trails or cohort studies comparing iNPH shunting with placebo or other treatment. Evidence was summarized using fixed and randomized effects frequentist meta-analysis when the $I^2$ was <50% and >50%, respectively. Subgroup analysis based on different study designs and surgical procedures was conducted to explore sources of heterogeneity. The sensitivity analyses were conducted by systematically excluding each study to determine the potential effect of individual studies on overall risk. Results: Eleven studies including 1417 participants were initially identified. All included randomized controlled trials had a high risk of bias, while cohort studies had a low risk of bias. Ventriculoperitoneal (VP) shunting was effective at decreasing the times of 10m walks (MD= -2.52, 95% CI: -4.78 to -0.26, $I^2$=0), while lumboperitoneal (LP) shunting was effective at improving cognitive level (MD=1.29, 95% CI: 1.09 to 1.49, $I^2$=0), 10 m walks (MD=-32.20, 95% CI: -48.07 to -16.33), and bladder control (MD=-0.25, 95% CI: -0.35 to -0.15, $I^2$=76). Regarding adverse events, the VP and LP groups showed no differences in subdural hematoma, intracranial infection, intracranial hemorrhage, tube-related complications, or seizures. Compared with VP shunting, ventriculoatrial shunting was associated with a higher risk of subdural hematoma. Conclusion: VP and LP are the best medical treatments for patients with iNPH.

**Keywords:** Idiopathic normal pressure hydrocephalus, shunting surgery, effectiveness, safety

## Introduction

Idiopathic normal-pressure hydrocephalus (iNPH) is a degenerative disease of the brain that presents with impaired motion, cognition, and urinary control (Hakim-Adams syndrome). Enlarged ventricles and narrow apical sulci are characteristic manifestations observed on computed tomography (CT) and magnetic resonance imaging (MRI), while spinal tap tests and brain pressure monitoring can assist in the diagnosis of iNPH. Alvi et al. reported that the incidence of iNPH in the United States ranges from 300,000 to 700,000 [1]. Some clinicians have suggested nonsurgical therapies for iNPH, such as acetazolamide, glucocorticoids, and neuroprotective drugs. However, these treatments have had limited success, and to date, no medicine for iNPH has yet been approved by the Food and Drug Administration [2]. Different treatments are applied for patients with iNPH, including ventriculoperitoneal (VP), ventriculoatrial (VA), and lumboperitoneal (LP) shunting, and third ventriculostomy (EVT). VP shunting is the current standard treatment for patients with iNPH; however, it is associated with a high-

https://doi.org/10.62347/MMPE6658

er risk of hemorrhage, seizures, and infections [3]. Conversely, in Japan, patients with iNPH prefer LP to VP [4]. Patients were more likely to undergo lumbar surgery than cranial surgery. However, LP has been reported to have higher rates of failure and symptomatic over-drainage [3]. Although VA shunting provides intraoperative confirmation of the placement and a consistent low-pressure outlet, it is associated with a higher risk of cardiopulmonary complications [5]. With the development of neuroendoscopy, EVT has become a widely-accepted treatment option for iNPH, as it does not require implant shunt surgery, and has a positive effect on disease course [6]. Although shunting surgeries are recommended for patients with iNPH according to practice guidelines in America, England, Japan, and China (Level C) [7-9], the vast majority of articles used to inform these guidelines were uncontrolled observational studies with low literature quality, which merely reported clinical improvement after shunt surgery with inconsistent results [10-12]. To date, there is a lack of high-level evidence evaluating the safety and efficacy of shunting surgery. Thus, this systematic review and meta-analysis aimed to evaluate the efficacy and safety of iNPH after different shunting surgery.

## Materials and methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reports of Systematic Review and Meta-Analysis (PRISMA) statements [13]. The protocol for this meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42023452623.

### *Search strategy*

We systematically searched four databases from inception until June 29, 2023: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. Medical Subject Headings and free-text search terms related to “Hydrocephalus, Normal Pressure”, “Ventriculoperitoneal Shunt”, and “Cerebrospinal Fluid Shunts” were used. We further tracked the references of the included studies and relevant systematic reviews and meta-analyses to identify additional potential studies. A detailed search strategy is presented in Supplementary Table 1. The language used was restricted to English. Our search did not apply restrictions on publication year or status.

### *Study selection*

We imported all searched citations into the EndNote X9 software, removing duplicate citations. Subsequently, we used Rayyan, an online literature management software, to manage and screen citations [14]. Trial screening was independently performed by two reviewers (Xiaowei Liu and Xiyuan Deng). When the decisions of the two reviewers were not in accordance, differences were resolved through consultation with a third reviewer (Bei Pan). We included randomized controlled trials and/or cohort studies to assess the efficacy and safety of idiopathic normal-pressure shunting in patients with iNPH. The diagnoses of iNPH were based on international guidelines (Supplementary Table 2) [15]. The outcomes of interest were as follows: reporting any outcome in at least one of the three clinical areas (e.g., gait, urinary incontinence, or cognition) and/or describing adverse events. We excluded studies that involved patients lacking sensory-motor skills and communication skills at baseline; that were case-control studies, cross-sectional studies, and systematic reviews and meta-analyses; studies without a control group or where the control group was the non-iNPH population.

### *Data extraction*

We created a standard data collection form for the reviewers to use when extracting the data. Two reviewers (Xiaowei Liu and Xiyuan Deng) independently extracted the following data: (1) general information of the included studies, including the name of the first author, country, year of publication, study design, type of intervention, and study duration; (2) baseline characteristics of the participants, including sex, age, smoking or diabetes condition, and sample size; and (3) outcomes of interest, including the scale of clinical areas (e.g., gait, urinary incontinence, or cognition) and adverse events. Conflicts of interest were resolved by a consensus.

### *Quality assessment*

Two reviewers (Xiaowei Liu and Xiyuan Deng) independently assessed the risk of bias of each

of the included randomized controlled trial (RCT) studies using a modified version of the Cochrane risk-of-bias tool [16], which used the following response options: 'definitely or probably yes' (assigned a low risk of bias) and 'definitely or probably no' (assigned a high risk of bias). Any conflicts of interest were resolved by a third reviewer (Bei Pan). Individual studies were classified as low-risk if all nine questions were low risk (definitely or probably low); otherwise, we considered them to have a high risk of bias [17]. Teams of two reviewers independently assessed the risk of bias of each cohort study using modified version of the Newcastle-Ottawa scale, comprising 8 questions [18], to which we used response options if 'definitely or probably yes' (assigned a low risk of bias) and 'definitely or probably no' (assigned a high risk of bias). Any conflicts were resolved through discussion or adjudication by a senior reviewer. We further clarified individual studies as having low risk or high risk of bias according to the following criteria: (1) if ≥5 of the 8 questions were low risk (definitely or probably yes), then studies were considered as having low risks; (2) if studies didn't meet the criteria for low risk of bias as detailed above, they were considered as having high risk [19, 20].

*Statistical analysis*

A meta-analysis was conducted using Review Manager software (Revman Version 5.4.1; Cochrane Collaboration, 2021) and Review Manager (version 5.4). The level of cognitive change was measured using different scales, and scores from different instruments were converted to the units of the reference scales [21]. We calculated the odds ratios (OR) with 95% confidence intervals (CIs) for dichotomous data, and the mean difference (MD) with 95% CIs for continuous data. If there were no events in one group, we calculated the rate difference (RD) instead of OR. Heterogeneity between the studies were judged based on $I^2$ and Dixons Q-test. A fixed-effects frequentist meta-analysis was conducted to summarize the evidence if the $I^2$ was <50%; otherwise, a randomized effect was used to summarize the evidence. Subgroup analysis was performed according to shunt type (VP vs. LP, RCT vs. cohort study). The sensitivity analyses were conducted by systematically excluding each study to determine the potential effect of individual studies on overall risk. The test for publication bias was not necessary to analyze, because the number of included trials was less than ten [22].

## Results

*Literature selection*

A total of 4117 studies were initially identified, of which 1800 were duplicates. After reviewing the titles and abstracts, 27 studies were selected for further review. Of these, 16 were excluded (wrong study design, 11; wrong population, 3; and wrong outcomes, 2). Finally, 11 articles met the inclusion criteria, including 4 RCTs and 7 cohort studies. Appendix 1 presents a list of studies excluded from the full-text screening. The detailed selection process is illustrated in **Figure 1**.

*Characteristics of the included studies*

**Table 1** summarizes the characteristics of the included studies, which comprised 11 articles, including four RCTs and seven cohort studies with 1417 participants (694 male and 723 women) from nine countries. Of these 11 studies, 2 each were conducted in China, the USA, and Japan, and all were published between 2009 and 2023. The median age was 75.4 years, the median proportion of women was 51.02%, and the median study period was three months.

*Risk of bias of individual*

**Figures 2** and **3** show the risks of bias for each of the RCT and cohort studies, respectively. Supplementary Tables 3 and 5 show the detailed guidelines for the risk of bias assessment. All included RCTs were evaluated as having a high risk of bias (Supplementary Table 6); the major limitation was the blind implementation. Conversely, all of the cohort studies evaluated had a low risk of bias (Supplementary Table 4).

*Clinical improvement*

**Table 2** summarizes the changes in clinical symptoms and adverse events following iNPH shunting.

*Cognitive impairment:* Eight articles, including 707 participants, reported on cognitive impairment. Six articles compared shunt surgery with placebo, and the results showed that shunt surgery could improve cognitive function

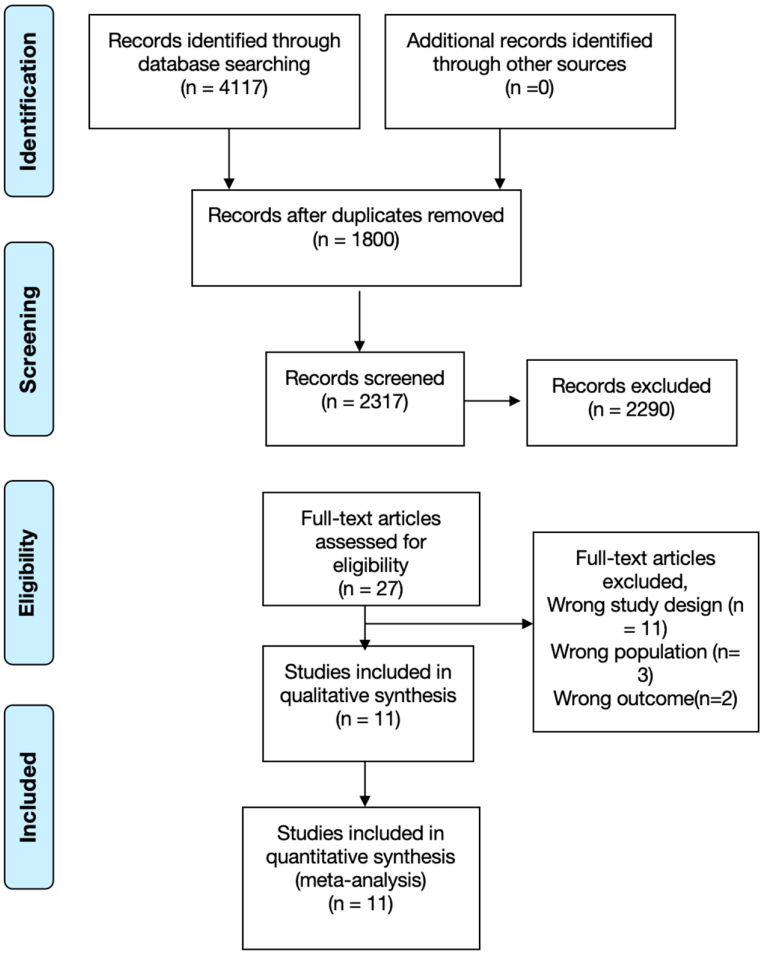



**Figure 1.** Study selection process.

(MD=1.41, 95% CI: 0.11 to 2.71, $I^2$=70%) (**Table 2** and Supplementary Figure 1). For the subgroup analysis of different shunt types, we found that VP showed no cognitive improvement compared to placebo, with high heterogeneity (MD=2.76, 95% CI: -1.62 to 7.14, $I^2$=87%), while LP achieved a better cognitive improvement than placebo (MD=1.29, 95% CI: 1.09 to 1.49, $I^2$=0) (**Table 2** and Supplementary Figure 1). We further performed a subgroup analysis according to study type. In the RCTs, VP showed no cognitive improvement compared with placebo (MD=0.11, 95% CI: -1.60 to 1.81, $I^2$=2) but LP improved cognitive function better than the placebo (MD=1.30, 95% CI: 1.10 to 1.50) (Supplementary Table 7 and Supplementary Figure 17). In the cohort studies, VP improved cognitive status (MD=5, 95% CI: 2.83 to 7.17), while LP achieved no cognitive improvement (MD=0.42, 95% CI: -1.36 to 2.20, $I^2$=0) (Supplementary Table 7 and Supplementary Figure 18). Three trials reported cognitive changes between the VP and LP, but there was no significant difference between the VP and LP groups (MD=0.19, 95% CI: -0.24 to 0.62, $I^2$=0) (**Table 2** and Supplementary Figure 2). Only one study, which of Pinto et al. [6], compared EVT and VP, finding that cognitive improvement in the EVT group was lower than that in the VP group after 3 months. However, this improvement was only partially maintained after 12 months of treatment. The sensitivity analysis revealed that excluding any individual study did not alter the overall results, indicating that the outcomes were consistent and reliable (Supplementary Figures 21 and 22).

*Gait disturbance:* Six articles including 261 patients reported on gait disturbances. Overall, shunt surgery showed no gait improvement on 10m walking time (MD= -12.56, 95% CI: -28.29 to 3.17, $I^2$=79%) (**Table 2** and Supplementary Figure 3) compared to placebo. For the subgroup analysis of different shunt types, we found that both VP (MD=-2.52, 95% CI: -4.78 to -0.26, $I^2$=0) and LP (MD=-32.20, 95% CI: -48.07 to -16.33) decreased the 10-meter walking times compared to the placebo (**Table 2** and Supplementary Figure 3). We further performed a subgroup analysis according to study type. In the RCT group, VP improved the 10 m times compared to placebo (MD= -2.51, 95% CI: -4.78 to -0.23, $I^2$=0) (Supplementary Table 7 and Supplementary Figure 19). In the cohort group, VP didn't improve the 10 m times compared to placebo (MD=-19.14, 95% CI: -46.61 to 8.33, $I^2$=76) (Supplementary Table 7 and Supplementary Figure 20). Pinto et al. [6] reported that motor improvement was greater with VP than with EVT. Sensitivity analysis indicated that heterogeneity mainly resulted from the Todisco et al. [36], which used LP to treat iNPH (Supplementary Figure 23).

**Table 1.** Baseline characteristics of selected articles

| Author year | Country | SEX M/F | Age (years, Range, mean ± SD) | Population | Intervention | Comparsion | Study period | Number of participants | Study type |
|---|---|---|---|---|---|---|---|---|---|
| Luciano [12] 2022 | USA | 8/10 | 74.2 (72.1, 76,6) | iNPH | VP | Placebo | 4 months | 18 | RCT |
| Xie [23] 2021 | China | 41/35 | 72.5±7.0 | iNPH | LP | VP | 6 months | 76 | Cohort |
| Nakajima [35] 2021 | Japan | 86/70 | 76 (72, 79) | iNPH | VP | LP | 3 months | 156 | Cohort |
| Todisco [36] 2020 | Italy | 45/33 | 76.2±5.6 | iNPH | LP | Placebo | 6 months | 78 | Cohort |
| Hung [37] 2017 | USA | 230/266 | 73.5 (34, 91) | iNPH | VA | VP | - | 496 | Cohort |
| Miyajima [4] 2016 | Japan | 80/103 | 75.4±5 | iNPH | LP | Placebo | 3 months | 183 | Cohort |
| Kazui [25] 2015 | Japan | 50/43 | 76.3±4.7 | iNPH | VA | VP | 3 months | 88 | RCT |
| McGovern [5] 2014 | USA | 100/87 | 75.6±8.4 | iNPH | VA | VP | - | 234 | Cohort |
| Goms [6] 2012 | Brazil | 24/18 | 70 (60, 75) | iNPH | EVT | VP | 3 months | 42 | RCT |
| Tisell [24] 2011 | Sweden | 9/5 | 75 (60, 82) | iNPH | VP | Placebo | 3 months | 14 | RCT |
| Razay [38] 2009 | Australia | 21/11 | 77.4 (58, 91) | iNPH | VP | Placebo | 3 months | 32 | Cohort |

iNPH: Idiopathic normal pressure hydrocephalus, VP: Ventriculoperitoneal, LP: Lumboperitoneal, EVT: Third Ventriculostomy, VA: Ventriculoatrial, M: Male, F: Famale.

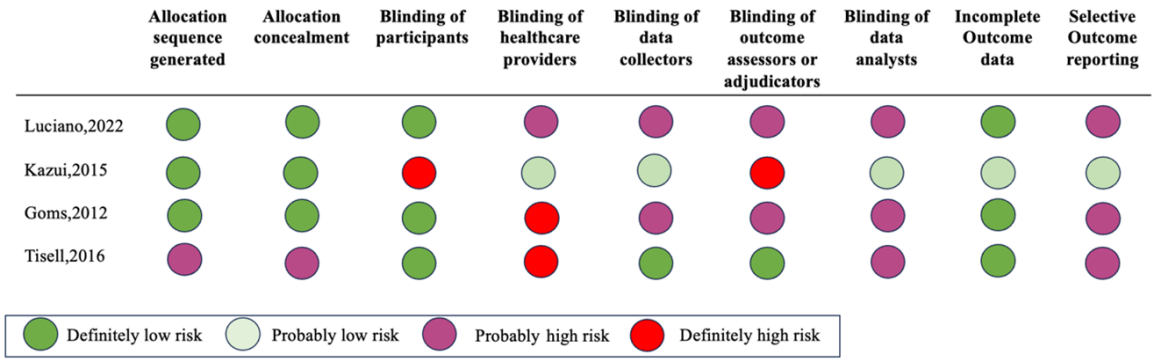



**Figure 2.** Results of risk of bias assessment for RCTs.

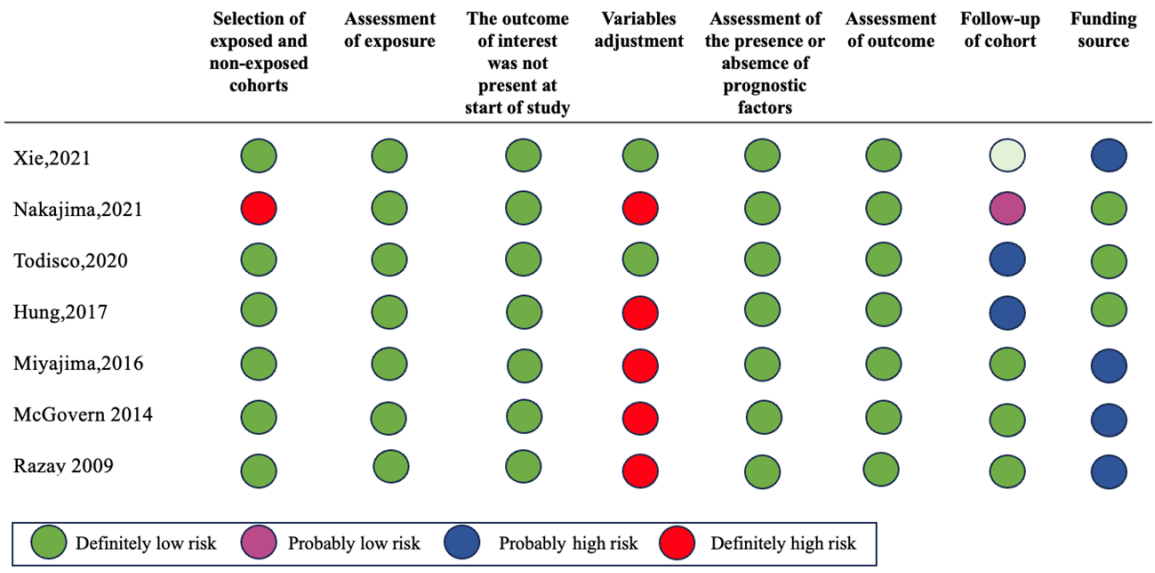



**Figure 3.** Results of risk of bias assessment for cohort studies.

*Bladder continence:* Five articles including 381 patients reported on bladder changes. In terms of bladder continence, LP decreased bladder symptoms compared with the placebo (MD= -0.25, 95% CI: -0.35 to -0.15, $I^2$=76) (**Table 2** and Supplementary Figure 4). Luciano et al.

**Table 2.** Summary results of clinical symptoms in this meta-analysis

| | | MD | 95% CI | $I^2$ |
|---|---|---|---|---|
| Cognitive improvement | Shunt vs. placebo | 1.41 | 0.11 to 2.71 | 70 |
| | VP vs. placebo | 2.76 | -1.62 to 7.14 | 87 |
| | LP vs. placebo | 1.26 | 1.09 to 1.49 | 0 |
| | VP vs. LP | 0.19 | -0.24 to 0.62 | 0 |
| Times of 10 m walks | Shunt vs. placebo | -12.56 | -28.29 to 3.17 | 79 |
| | VP vs. placebo | -2.52 | -4.78 to -0.26 | 0 |
| | LP vs. placebo | -32.2 | -48.07 to -16.33 | - |
| Urinary symptoms | LP vs. placebo | -0.25 | -0.35 to -0.15 | 76 |

VP: Ventriculoperitoneal, LP: Lumboperitoneal.

**Table 3.** Summary result of adverse events in this meta-analysis

| | | OR/RD | 95% CI | $I^2$ |
|---|---|---|---|---|
| SH | Shunt vs. placebo | 4.12 | 0.43 to 39.5 | 0 |
| | VP vs. LP | 0.02 | -0.02 to 0.05 | 0 |
| | VA vs. VP | 2.16 | 1.20 to 3.87 | 0 |
| SH need surgery | Shunt vs. placebo | 0.04 | -0.03 to 0.11 | 0 |
| Infection | VP vs. LP | -0.01 | -0.03 to 0.02 | 0 |
| | VA vs. VP | 0.48 | 0.12 to 1.86 | 0 |
| Hemorrhage | VP vs. LP | 6.40 | 0.77 to 52.91 | 0 |
| | VA vs. VP | 2.70 | 0.81 to 8.98 | 0 |
| Tube blockage | VP vs. LP | -0.01 | -0.03 to 0.02 | 0 |
| Tube revision | VP vs. LP | 0.27 | 0.01 to 5.02 | 53 |
| | VA vs. VP | 0.42 | 0.22 to 0.80 | 0 |

VP: Ventriculoperitoneal, LP: Lumboperitoneal, VA: Ventriculoatrial, SH: subdural hematoma.

[12] found that bladder continence symptoms in the VP group were improved compared to the placebo group. Miyajima et al. [4] found that changes in urinary symptoms were not statistically different between the VPS and LPS groups.

*Adverse events*

*Subdural hematoma:* Seven studies involving 1141 patients reported on the occurrence of subdural hematoma (SH). Compared with placebo, shunt surgery did not increase risk of SH (OR=4.12, 95% CI: 0.43 to 39.05, $I^2$=0) (**Table 3** and Supplementary Figure 5) and or the need for SH surgery (RD=0.04, 95% CI: -0.03 to 0.11, $I^2$=0) (Supplementary Figure 6). The LP and VP showed no differences in the occurrence of SH (RD=0.02, 95% CI: -0.02 to 0.05, $I^2$=0) (Supplementary Figure 7); however, VA was associated with a higher risk of SH (OR=2.16, 95% CI: 1.20 to 3.87, $I^2$=0) (Supplementary Figure 8), but showed no difference in subdural hygroma (OR=1.16, 95% CI: 0.65 to 2.05, $I^2$=0) (Supplementary Figure 9) compared to VP. Pinto et al. [6] reported no differences between EVT and VP.

*Intracranial infection:* Five articles, including 1035 patients, reported intracranial infections. VP and LP showed no difference in the risk of infection (RD=-0.01, 95% CI: -0.03 to 0.02, $I^2$=0) (**Table 3** and Supplementary Figure 10), nor did VA and VP (OR=0.48, 95% CI: 0.12 to 1.86, $I^2$=0) (**Table 3** and Supplementary Figure 11). Pinto et al. [6] reported no difference in the incidence of infection between EVT and VP.

*Intracranial hemorrhage:* Six articles, including 1053 patients, reported on intracranial hemorrhage. LP and VP showed no difference in the risk of the occurrence of hemorrhage (OR=6.40, 95% CI: 0.77 to 52.91, $I^2$=0) (**Table 3** and Supplementary Figure 12), nor did VA and VP (OR=2.70, 95% CI: 0.81 to 8.98, $I^2$=0) (**Table 3** and Supplementary Figure 13). Lucino et al. [12] reported no differences in the intracranial

occurrence between shunt surgery and placebo. Pinto et al. [6] reported no difference in the incidence of hemorrhage between EVT and VP.

*Tube-related complications:* Five articles including 1081 patients reported on tube-related complications. VP and LP showed no differences in the rates of tube blockage (RD=-0.01, 95% CI: -0.03 to 0.02, $I^2$=0) (**Table 3** and Supplementary Figure 14) or revision (OR=0.27, 95% CI: 0.01 to 5.02, $I^2$=53) (Supplementary Figure 15). Compared to VP, VA was associated with a lower risk of tube revision complications (OR=0.42, 95% CI: 0.22 to 0.80, $I^2$=0) (**Table 3** and Supplementary Figure 16).

*Seizures:* In terms of seizures, Xie et al. [23] enrolled 76 patients who underwent VPs or LPs, finding no seizure complications in either group. McGovern et al. [5] compared seizure complications between the VA and VP groups, finding no differences.

## Discussion

This systematic review and meta-analysis of four randomized controlled trials (RCTs) and seven cohort studies involving 1417 participates first assessed the safety and efficacy of different shunt surgeries. The results of this systematic review showed that, compared with a placebo, shunt surgery improved cognitive impairment, but not gait disturbance. We further performed a subgroup analysis according to surgical method and study type. Subgroup analysis revealed that LP showed better cognitive improvement and urinary symptom improvement than the placebo, while both LP and VP improved gait disturbance; in terms of adverse events, VA was more likely to cause SH than VP. The VP and LP groups showed no significant differences in the occurrence of SH, infection, hemorrhage, tube blockage, and tube revision.

Our meta-analysis included only four RCTs. Luciano and Tisell enrolled 18 and 14 patients, respectively, to compare the effectiveness and safety of VP with placebo respectively [12, 24]. Lucaiano et al. further found that VP was beneficial at improving gait disturbances, showing no statistical difference in cognitive improvement [12]. Tisell found that shunt surgery was beneficial in improving psychometric performance and gait [24]. However, these two articles only enrolled a few patients with iNPH, and had a high risk of bias, which resulted in a low reliability of the results. Fernando Campos Gomes Pinto [6] conducted an RCT that enrolled 42 patients randomized to the EVT and VPS groups. The VPS group showed better improvements in functional neurological outcomes than the EVT group. They proposed that EVT was not the best treatment for iNPH. However, the long-term outcomes of EVT and VPS placement have not yet been described. Kazwi found that LPS was beneficial to cognition, motion, and urinary function compared with a placebo [25].

Giordan [10] conducted a meta-analysis to evaluate improvements in clinical symptoms and the occurrence of complications in patients with iNPH in 2018. First, this meta-analysis only investigated the occurrence rates of symptom improvement and complications in patients with iNPH, without comparing the differences between each group. However, owing to the lack of universal scales to evaluate effectiveness, especially with regard to cognition, motion, and urinary function, selection bias was inevitable. To the best of our knowledge, this meta-analysis is the most up-to-date and extensive review of the effectiveness and safety of iNPH shunting.

Increased CSF pulsatility and reduced CSF drainage result in ventriculomegaly, which causes regional and global hypoperfusion. This vital pathophysiology initiates a series of brain damaging pathways, including blood-brain barrier (BBB) disruption, metabolism disturbance, astrogliosis, and neuroinflammation, all of which result in white and grey matter injury. These are the pathophysiology and clinical manifestations of iNPH [26]. Surgery generally involves the reversal of abnormal CSF dynamics. Placement of a cerebral shunt and its location is based on surgeon's preference. Surgeons always choose the frontal approach to the anterior horn or the parieto-occipital approach to the trigone or occipital horn. A catheter placed in the cerebral ventricle is referred to as a proximal shunt. The preferred proximal shunt was located in the right lateral ventricle, which is not the dominant hemisphere in most patients. If the ventricle is asymmetrical, the surgeons generally select a larger ventricle. The distal catheter can be placed in the abdomen or heart, which is termed the VP or VA. LP is a

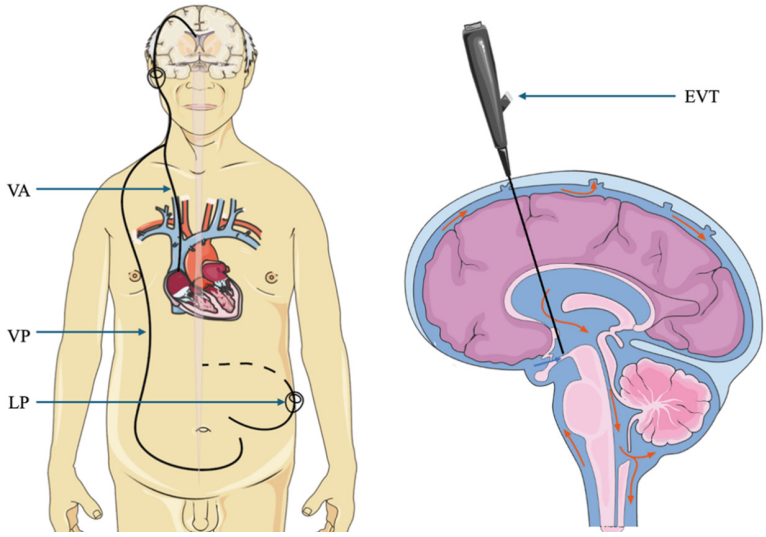



**Figure 4.** The simple graph of VA, VP, LP and EVT. VP: Ventriculoperitoneal, VA: Ventriculoatrial, LP: Lumboperitoneal, EVT: Third Ventriculostomy.

shunt surgery in which the proximal shunt is in the lumbar vertebra and the distal catheter is in the abdomen (**Figure 4**). Gait disorders have been reported to be associated with frontal subcortical circuits and periventricular white matter. These symptoms can be improved by mechanical CSF decompression via shunt surgery [27]. Cognitive impairment and urinary symptoms are associated with more extensive brain networks, such as those of the hippocampus, and other potential concomitant neurodegenerative changes, which may be less pronounced [28].

Regarding complications, studies have reported that over-shunting, intracranial infection, intracranial hemorrhage and tube-related complications were the most frequent complications associated with shunt surgery [29]. SH was reported to be correlated with low valve pressure and poor ability of the cerebral cortex, which resulted in tearing of the bridging veins [30]. The cause of ICH was reported to be correlated with repeated puncture, abnormal shunt positioning, the barrier of venous return, shunt pressure change might result in intracranial hemorrhage. Intracranial infection mainly results from extensive intraoperative exposure and an unstrict aseptic technique [31]. Blockage of the proximal shunts may be caused by clots, brain tissue fragments, the choroid plexus, or improper location of the ventricle. The distal catheter was likely parceled by the omentum majus and discounted into the abdomen. Blockage of the divert pump results mainly from clots [32]. Seizures may result from an injury to the cerebral cortex, which produces a bodily stress response [33].

EVT uses a ventriculoscope to create an artificial path at the base of the third ventricle, shuttling CSF directly from the third ventricle to the basal subarachnoid space, bypassing the aqueduct and CSF pathway of the posterior fossa (**Figure 4**). EVT is thus considered as an internal shunt procedure. As EVT is free from shunts, some surgeons have suggested the application of EVT for iNPH. Indeed, EVT is already a standard treatment for obstructive hydrocephalus. EVT can increase the systolic outflow from the ventricles and decrease the intraventricular pulse pressure, thereby decreasing the width of the ventricles. This dilates the compressed vessels and increases intracranial compliance. Dilated capillaries would increase the blood flow and CSF absorption. In 2008, an Italian multicenter retrospective study of 110 patients with iNPH reported that 69.1% of patients were benefited from EVT [34]. Patent subarachnoid spaces and adequate CSF resorption are necessary for successful surgery.

Our meta-analysis is the first to evaluate the effectiveness of iNPH shunting on patients' cognitive, motor, and urinary symptoms. This systematic review and meta-analysis included a comprehensive search strategy with explicit eligibility criteria and an evaluation of the risk of bias using uniform criteria. Furthermore, we performed this analysis in accordance with the PRISMA guidelines to ensure higher reporting quality. However, some limitations of this study should be acknowledged when analyzing the results. Firstly, our meta-analysis employed different clinical scales to evaluate the effectiveness of iNPH shunting, which may have resulted in heterogeneity. Therefore, a universally accepted grading system for evaluating treatment outcomes should be established world-

wide. Our meta-analysis further enrolled only 11 articles; as such, we did not perform a subgroup analysis to evaluate the different types of divert valves affected by iNPH. Further, our meta-analysis enrolled only four RCTs that may not have had the highest evidence grade. In the future, more RCTs should be conducted in clinics to assess the effectiveness and safety of iNPH shunting. When assessing clinical improvement, different clinical assessors may produce different results, which may cause heterogeneity. Our meta-analysis excluded studies published in non-English languages, which may have resulted in language bias. As such, we call for additional native speakers of non-English languages to conduct similar studies.

## Acknowledgements

This work was supported by the Sichuan Provincial Medical Association Orthopedics Special Research Project (2020SAT18).

## Disclosure of conflict of interest

None.

**Address correspondence to:** Yongxiu Yang, Department of The First Hospital of Lanzhou University, Lanzhou 730000, Gansu, China. E-mail: yxyanglzu@163.com; Kehu Yang, Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, No. 199 Donggang West Road, Chengguan District, Lanzhou 730000, Gansu, China. E-mail: yangkh-ebm@lzu.edu.cn

## References

[1] Alvi MA, Brown D, Yolcu Y, Zreik J, Javeed S, Bydon M, Cutsforth-Gregory JK, Graff-Radford J, Jones DT, Graff-Radford NR, Cogswell PM and Elder BD. Prevalence and trends in management of idiopathic normal pressure hydrocephalus in the united states: insights from the national inpatient sample. World Neurosurgery 2021; 145: E38-E52.

[2] Del Bigio MR and Di Curzio DL. Nonsurgical therapy for hydrocephalus: a comprehensive and critical review. Fluids Barriers CNS 2016; 13: 3.

[3] Karabatsou K, Quigley G, Buxton N, Foy P and Mallucci C. Lumboperitoneal shunts: are the complications acceptable? Acta Neurochirurgica 2004; 146: 1193-1197.

[4] Miyajima M, Kazui H, Mori E and Ishikawa M; on behalf of the SINPHONI-2 Investigators. One-year outcome in patients with idiopathic normal-pressure hydrocephalus: comparison of lumboperitoneal shunt to ventriculoperitoneal shunt. J Neurosurg 2016; 125: 1483-1492.

[5] McGovern RA, Kelly KM, Chan AK, Morrissey NJ and McKhann GM 2nd. Should ventriculoatrial shunting be the procedure of choice for normal-pressure hydrocephalus? J Neurosurg 2014; 120: 1458-1464.

[6] Pinto FC, Saad F, de Oliveira MF, Pereira RM, de Miranda FL, Tornai JB, Lopes MI, Ribas ES, Valinetti EA and Teixeira MJ. Role of endoscopic third ventriculostomy and ventriculoperitoneal shunt in idiopathic normal pressure hydrocephalus: preliminary results of a randomized clinical trial. Neurosurgery 2013; 72: 845-853.

[7] Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G and Gloss D. Practice guideline: idiopathic normal pressure hydrocephalus: response to shunting and predictors of response: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology. Neurology 2015; 85: 2063-2071.

[8] Nakajima M, Yamada S, Miyajima M, Ishii K, Kuriyama N, Kazui H, Kanemoto H, Suehiro T, Yoshiyama K, Kameda M, Kajimoto Y, Mase M, Murai H, Kita D, Kimura T, Samejima N, Tokuda T, Kaijima M, Akiba C, Kawamura K, Atsuchi M, Hirata Y, Matsumae M, Sasaki M, Yamashita F, Aoki S, Irie R, Miyake H, Kato T, Mori E, Ishikawa M, Date I and Arai H. Guidelines for management of idiopathic normal pressure hydrocephalus (Third Edition): endorsed by the Japanese society of normal pressure hydrocephalus. Neurol Med Chir (Tokyo) 2021; 61: 63-97.

[9] Wu J, Lu AD, Zhang LP, Zuo YX and Jia YP. Study of clinical outcome and prognosis in pediatric core binding factor-acute myeloid leukemia. Zhonghua Xue Ye Xue Za Zhi 2019; 40: 52-57.

[10] Giordan E, Palandri G, Lanzino G, Murad MH and Elder BD. Outcomes and complications of different surgical treatments for idiopathic normal pressure hydrocephalus: a systematic review and meta-analysis. J Neurosurg 2018; 131: 1024-1036.

[11] Kanno S, Saito M, Kashinoura T, Nishio Y, Iizuka O, Kikuchi H, Takagi M, Iwasaki M, Takahashi S and Mori E. A change in brain white matter after shunt surgery in idiopathic normal pressure hydrocephalus: a tract-based spatial statistics study. Fluids Barriers CNS 2017; 14: 1.

[12] Luciano M, Holubkov R, Williams MA, Malm J, Nagel S, Moghekar A, Eklund A, Zwimpfer T, Katzen H, Hanley DF and Hamilton MG; PENS Co-investigators and AHCRN Site PIs. Placebo-controlled effectiveness of idiopathic normal

pressure hydrocephalus shunting: a randomized pilot trial. Neurosurgery 2023; 92: 481-489.
[13] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gøtzsche PC, Dickersin K, Boutron I, Altman DG and Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015; 162: 777-784.
[14] Ouzzani M, Hammady H, Fedorowicz Z and Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016; 5: 210.
[15] Marmarou A, Bergsneider M, Relkin N, Klinge P and Black PM. Development of guidelines for idiopathic normal-pressure hydrocephalus: introduction. Neurosurgery 2005; 57: 1-3.
[16] Partners E. Methodological resources. 2011.
[17] Pan B, Ge L, Lai H, Hou L, Tian C, Wang Q, Yang K, Lu Y, Zhu H, Li M, Wang D, Li X, Zhang Y, Gao Y, Liu M, Ding G, Tian J and Yang K. The comparative effectiveness and safety of insomnia drugs: a systematic review and network meta-analysis of 153 randomized trials. Drugs 2023; 83: 587-619.
[18] Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, Losos M and Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2000; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[19] Zeraatkar D, Han MA, Guyatt GH, Vernooij RWM, El Dib R, Cheung K, Milio K, Zworth M, Bartoszko JJ, Valli C, Rabassa M, Lee Y, Zajac J, Prokop-Dorner A, Lo C, Bala MM, Alonso-Coello P, Hanna SE and Johnston BC. Red and processed meat consumption and risk for all-cause mortality and cardiometabolic outcomes: a systematic review and meta-analysis of cohort studies. Ann Intern Med 2019; 171: 703-710.
[20] Pan B, Ge L, Lai H, Wang Q, Wang Q, Zhang Q, Yin M, Li S, Tian J, Yang K and Wang J. Association of soft drink and 100% fruit juice consumption with all-cause mortality, cardiovascular diseases mortality, and cancer mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. Crit Rev Food Sci Nutr 2022; 62: 8908-8919.
[21] Ebrahim S, Johnston BC, Akl EA, Mustafa RA, Sun X, Walter SD, Heels-Ansdell D, Alonso-Coello P and Guyatt GH. Addressing continuous data measured with different instruments for participants excluded from trial analysis: a guide for systematic reviewers. J Clin Epidemiol 2014; 67: 560-570.
[22] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rucker G, Harbord RM, Schmid CH, Tetzlaff J, Deeks JJ, Peters J, Macaskill P, Schwarzer G, Duval S, Altman DG, Moher D and Higgins JP. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 343: d4002.
[23] Xie D, Chen H, Guo X and Liu Y. Comparative study of lumboperitoneal shunt and ventriculoperitoneal shunt in the treatment of idiopathic normal pressure hydrocephalus. Am J Transl Res 2021; 13: 11917-11924.
[24] Tisell M, Tullberg M, Hellstrom P, Edsbagge M, Hogfeldt M and Wikkelso C. Shunt surgery in patients with hydrocephalus and white matter changes. J Neurosurg 2011; 114: 1432-1438.
[25] Kazui H, Miyajima M, Mori E and Ishikawa M; SINPHONI-2 Investigators. Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial. Lancet Neurol 2015; 14: 585-594.
[26] Wang Z, Zhang Y, Hu F, Ding J and Wang X. Pathogenesis and pathophysiology of idiopathic normal pressure hydrocephalus. CNS Neurosci Ther 2020; 26: 1230-1240.
[27] Tang YM, Yao Y, Xu S, Li X, Hu F, Wang H, Ding J and Wang X. White matter microstructural damage associated with gait abnormalities in idiopathic normal pressure hydrocephalus. Front Aging Neurosci 2021; 13: 660621.
[28] Eide PK and Ringstad G. Delayed clearance of cerebrospinal fluid tracer from entorhinal cortex in idiopathic normal pressure hydrocephalus: a glymphatic magnetic resonance imaging study. J Cereb Blood Flow Metab 2019; 39: 1355-1368.
[29] Wong JM, Ziewacz JE, Ho AL, Panchmatia JR, Bader AM, Garton HJ, Laws ER and Gawande AA. Patterns in neurosurgical adverse events: cerebrospinal fluid shunt surgery. Neurosurg Focus 2012; 33: E13.
[30] Panagopoulos D, Stranjalis G, Gavra M, Boviatsis E and Korfias S. Shunt over-drainage, slit ventricle syndrome, programmable valves and anti-siphon devices. A narrative review of a multifactorial and intractable problem. J Integr Neurosci 2022; 21: 84.
[31] Hasbun R. Healthcare-associated ventriculitis: current and emerging diagnostic and treatment strategies. Expert Rev Anti Infect Ther 2021; 19: 993-999.
[32] Donaldson L, Côté E and Margolin E. Positional obstruction of ventriculoperitoneal shunt in a patient with idiopathic intracranial hypertension. J Neuroophthalmol 2022; 42: e588-e590.

[33] Hamouda AM, Pennington Z, Shafi M, Astudillo Potes MD, Hallak H, Graff-Radford J, Jones DT, Botha H, Cutsforth-Gregory JK, Cogswell PM and Elder BD. Ventriculoperitoneal shunt placement safety in idiopathic normal pressure hydrocephalus: anticoagulated versus non-anticoagulated patients. World Neurosurg 2024; 186: e622-e629.

[34] Gangemi M, Maiuri F, Naddeo M, Godano U, Mascari C, Broggi G and Ferroli P. Endoscopic third ventriculostomy in idiopathic normal pressure hydrocephalus. Neurosurgery 2008; 63: 62-69.

[35] Nakajima M, Yamada S, Miyajima M, Kawamura K, Akiba C, Kazui H, Mori E and Ishikawa M; SINPHONI-2 Investigators. Tap test can predict cognitive improvement in patients with iNPH-results from the multicenter prospective studies SINPHONI-1 and -2. Front Neurol 2021; 12: 769216.

[36] Todisco M, Picascia M, Pisano P, Zangaglia R, Minafra B, Vitali P, Rognone E, Pichiecchio A, Ceravolo R, Vanacore N, Fasano A and Pacchetti C. Lumboperitoneal shunt in idiopathic normal pressure hydrocephalus: a prospective controlled study. J Neurol 2020; 267: 2556-2566.

[37] Hung AL, Vivas-Buitrago T, Adam A, Lu J, Robison J, Elder BD, Goodwin CR, Jusue-Torres I and Rigamonti D. Ventriculoatrial versus ventriculoperitoneal shunt complications in idiopathic normal pressure hydrocephalus. Clin Neurol Neurosurg 2017; 157: 1-6.

[38] Razay G, Vreugdenhil A and Liddell J. A prospective study of ventriculo-peritoneal shunting for idiopathic normal pressure hydrocephalus. J Clin Neurosci 2009; 16: 1180-1183.

# Supplementary Materials

**Supplementary Table 1.** Detailed search strategy

| Databases [Platform] *Searches run* July 14 *2023* | | Results |
|---|---|---|
| PubMed < > | | 1503 |
| Cochrane Central Register of Controlled Trials < > | | 89 |
| Embase < > | | 1178 |
| Web of Science (SCI+SSCI) | | 1347 |
| TOTAL | | 4117 |
| Duplicate | | 1800 |
| Database: *Cochrane*<July 14 *2023*>89 | | |
| Search Strategy: | | |
| # | Searches | Results |
| #1 | MeSH descriptor: [Hydrocephalus, Normal Pressure] explode all trees | 59 |
| #2 | (Hydrocephalus, Normal-Pressure):ti,ab,kw OR (Normal Pressure Hydrocephalus):ti,ab,kw OR (NPH):ti,ab,kw OR (NPHs):ti,ab,kw OR (iNPH):ti,ab,kw | 1064 |
| #3 | (sNPH):ti,ab,kw OR (Hakim Syndrome):ti,ab,kw OR (Hakim Syndromes):ti,ab,kw OR (Syndrome, Hakim):ti,ab,kw OR (Syndromes, Hakim):ti,ab,kw | 12 |
| #4 | (Hakim's Syndrome):ti,ab,kw OR (Hakim's Syndromes):ti,ab,kw OR (Hakims Syndrome):ti,ab,kw OR (Syndrome, Hakim's):ti,ab,kw OR (Syndromes, Hakim's):ti,ab,kw | 10 |
| #5 | (normotensive hydrocephalus):ti,ab,kw OR (dement*):ti,ab,kw OR (dementia):ti,ab,kw | 16921 |
| #6 | #1 OR #2 OR #3 OR #4 OR #5 | 17908 |
| #7 | MeSH descriptor: [Ventriculoperitoneal Shunt] explode all trees | 84 |
| #8 | (Shunt, Ventriculoperitoneal):ti,ab,kw OR (Shunts, Ventriculoperitoneal):ti,ab,kw OR (Ventriculoperitoneal Shunts):ti,ab,kw OR (Ventriculo-peritoneal Shunt):ti,ab,kw OR (Shunt, Ventriculo-peritoneal):ti,ab,kw | 214 |
| #9 | (Shunts, Ventriculo-peritoneal):ti,ab,kw OR (Ventriculo peritoneal Shunt):ti,ab,kw OR (Ventriculo-peritoneal Shunts):ti,ab,kw | 30 |
| #10 | MeSH descriptor: [Cerebrospinal Fluid Shunts] explode all trees | 220 |
| #11 | (Shunts, Cerebrospinal Fluid):ti,ab,kw OR (Cerebrospinal Fluid Shunt):ti,ab,kw OR (Shunt, Cerebrospinal Fluid):ti,ab,kw | 241 |
| #12 | #7 OR #8 OR #9 OR #10 OR #11 | 402 |
| #13 | #12 AND #6 | 89 |
| Database: *PubMed*<July 14 *2023*>1503 | | |
| Search Strategy: | | |
| # | Searches | Results |
| #1 | "Hydrocephalus, Normal Pressure" [Mesh] | 2703 |
| #2 | ((((((((((((((((((Hydrocephalus, Normal-Pressure[Title/Abstract]) OR (Normal Pressure Hydrocephalus[Title/Abstract])) OR (NPH[Title/Abstract])) OR (NPHs[Title/Abstract])) OR (iNPH[Title/Abstract])) OR (sNPH[Title/Abstract])) OR (Hakim Syndrome[Title/Abstract])) OR (Hakim Syndromes[Title/Abstract])) OR (Syndrome, Hakim[Title/Abstract])) OR (Syndromes, Hakim[Title/Abstract])) OR (Hakim's Syndrome[Title/Abstract])) OR (Hakim's Syndromes[Title/Abstract])) OR (Hakims Syndrome[Title/Abstract])) OR (Syndrome, Hakim's[Title/Abstract])) OR (Syndromes, Hakim's[Title/Abstract])) OR (normotensive hydrocephalus[Title/Abstract])) OR (dement*[Title/Abstract])) OR (dementia/[Title/Abstract]) | 153313 |
| #3 | #1 OR #2 | 153713 |
| #4 | "Ventriculoperitoneal Shunt"[Mesh] | 4,891 |
| #5 | "Cerebrospinal Fluid Shunts"[Mesh] | 13,964 |
| #6 | ((((((((((Shunt, Ventriculoperitoneal[Title/Abstract]) OR (Shunts, Ventriculoperitoneal[Title/Abstract])) OR (Ventriculoperitoneal Shunts[Title/Abstract])) OR (Ventriculo-peritoneal Shunt[Title/Abstract])) OR (Shunt, Ventriculo-peritoneal[Title/Abstract])) OR (Shunts, Ventriculo-peritoneal[Title/Abstract])) OR (Ventriculo peritoneal Shunt[Title/Abstract])) OR (Ventriculo-peritoneal Shunts[Title/Abstract])) OR (Shunts, Cerebrospinal Fluid[Title/Abstract])) OR (Cerebrospinal Fluid Shunt[Title/Abstract])) OR (Shunt, Cerebrospinal Fluid[Title/Abstract]) | 2,587 |

| | | |
|---|---|---|
| #7 | #4 OR #5OR #6 | 14,809 |
| #8 | #7 AND #3 | 1503 |
| Database: *Embase*<July 14 *2023*>1178 | | |
| Search Strategy: | | |
| # | Searches | Results |
| #1 | 'normotensive hydrocephalus'/exp | 4856 |
| #2 | 'hydrocephalus, normal-pressure':ab,ti OR 'normal pressure hydrocephalus':ab,ti OR nph:ab,ti OR nphs:ab,ti OR inph:ab,ti OR snph:ab,ti OR 'hakim syndrome':ab,ti OR 'hakim syndromes':ab,ti OR 'syndrome, hakim':ab,ti OR 'syndromes, hakim':ab,ti OR 'hakims syndromes':ab,ti OR 'hakims syndrome':ab,ti OR 'syndrome, hakims':ab,ti OR 'syndromes, hakims':ab,ti OR 'normotensive hydrocephalus':ab,ti OR dement*:ab,ti OR dementia:ab,ti | 212852 |
| #3 | #1 OR #2 | 213705 |
| #4 | 'brain ventricle peritoneum shunt'/exp | 13143 |
| #5 | 'cerebrospinal fluid drainage system'/exp | 2104 |
| #6 | 'shunt, ventriculoperitoneal':ab,ti OR 'shunts, ventriculoperitoneal':ab,ti OR 'ventriculoperitoneal shunts':ab,ti OR 'ventriculo-peritoneal shunt':ab,ti OR 'shunt, ventriculo-peritoneal':ab,ti OR 'shunts, ventriculo-peritoneal':ab,ti OR 'ventriculo peritoneal shunt':ab,ti OR 'ventriculo-peritoneal shunts':ab,ti OR 'shunts, cerebrospinal fluid':ab,ti OR 'cerebrospinal fluid shunt':ab,ti OR 'shunt, cerebrospinal fluid':ab,ti | 2905 |
| #7 | #4 OR #5 OR #6 | 15728 |
| #8 | #3 AND #7 | 1178 |
| Database: *Web of Science* <July 14 2023>1347 | | |
| Science Citation Index Expanded (SCI-EXPANDED) - from 1980 to now | | |
| Social Sciences Citation Index (SSCI) - from 1980 to now | | |
| Search Strategy: | | |
| # | Searches | Results |
| #1 | ((((((((((((((((((((TS=(Hydrocephalus, Normal Pressure)) OR TS=(Normal Pressure Hydrocephalus)) OR TS=(NPH)) OR TS=(NPHs)) OR TS=(iNPH)) OR TS=(NPHs)) OR TS=(iNPH)) OR TS=(sNPH))) OR TS=(Hakim Syndrome)) OR TS=(Hakim Syndromes)) OR TS=(Syndrome, Hakim)) OR TS=(Syndromes, Hakim)) OR TS=(Hakim's Syndrome)) OR TS=(Hakim's Syndromes)) OR TS=(Hakims Syndrome)) OR TS=(Syndrome, Hakim's)) OR TS=(Syndromes, Hakim's)) OR TS=(normotensive hydrocephalus)) OR TS=(dement*)) OR TS=(dementia) | 207412 |
| #2 | ((((((((((((TS=(Ventriculoperitoneal Shunt)) OR TS=(Shunt, Ventriculoperitoneal)) OR TS=(Shunts, Ventriculoperitoneal)) OR TS=(Ventriculoperitoneal Shunts)) OR TS=(Ventriculo-peritoneal Shunt)) OR TS=(Shunt, Ventriculo-peritoneal)) OR TS=(Shunts, Ventriculo-peritoneal)) OR TS=(Ventriculo peritoneal Shunt)) OR TS=(Ventriculo-peritoneal Shunts)) OR TS=(Cerebrospinal Fluid Shunts)) OR TS=(Shunts, Cerebrospinal Fluid)) OR TS=(Cerebrospinal Fluid Shunt)) OR TS=(Shunt, Cerebrospinal Fluid) | 9029 |
| #3 | #1 AND #2 | 1347 |

**Supplementary Table 2.** Idiopathic normal-pressure hydrocephalus (iNPH) diagnosis

| History | Brain imaging | Clinical features | Supplementary test |
|---|---|---|---|
| 1. Insidious onset<br>2. A minimum duration of at least 3 to 6 months<br>3. No evidence of an antecedent event such as head trauma, intracerebral hemorrhage, meningitis, or other known causes of secondary hydrocephalus<br>4. Progression over time | 1. Ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evans >0.3)<br>2. No macroscopic obstruction to CSF flow | 1. Gait impairment (such as decreased step height/length/cadence and so on)<br>2. Cognitive impairment<br>3. Urinary symptoms (not attributed to primary urological disorders) | Large volume lumbar puncture (+)<br>or extended CSF drainage (+) |

**Supplementary Table 3.** Detailed guidance for assessment of risk of bias (cohort study)

| Item | Instruction | |
|---|---|---|
| Was selection of exposed and non-exposed cohorts drawn from the same population? | Definitely Yes | Studies in which selection for participation is not dependent on exposure level. For example, the European Prospective Investigation into Cancer and Nutrition study participants who were Recruited between January 1, 1992, and December 31,2000, predominantly from the general populations of 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). |
| | Probably Yes | / |
| | Probably No | / |
| | Definitely No | Studies that compare sugar-sweetened beverage and artificially sweetened beverage populations but draw sugar-sweetened beverage population from a different cohort. For example, a study may report on the EPIC-Oxford cohort but also include a subsample of participants from the Oxford Vegetarian Study. The study may then compare sugar-sweetened beverage population from the EPIC-Oxford cohort with artificially sweetened beverage populations from Oxford Vegetarian study. |
| Can we be confident in the assessment of exposure? | Definitely Yes | Participants complete sugar beverage measures at least once every five years. The sugar beverage measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has undergone validation against a weighted food record specifically for sugar beverage. |
| | Probably Yes | Participants complete a dietary measure at least once every six to eight years. The dietary measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has undergone validation against a dietary measure other than a weighted food record (e.g., 24 h food record, biomarker). Some studies may provide a citation to the study validating the dietary measure and other studies may simply say that the measure has been validated against another dietary measure. |
| | Probably No | Participants complete a dietary measure at least once every nine to 10 years. The dietary measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has not undergone any validation or the authors of the study do not report on the validity of the dietary measure. |
| | Definitely No | Participants complete a dietary measure only at baseline. The dietary measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has not undergone any validation or the authors of the study do not report on the validity of the dietary measure. Some studies may report that diet was assessed at multiple time points throughout the trial but only baseline dietary data is used for analysis. |
| Can we be confident that the outcome of interest was not present at the start of study? | Definitely Yes | The outcome of interest is fatal. In that case, we can be certain that participants did not have the outcome at baseline. |
| | Probably Yes | The authors have made an effort to exclude participants with the outcome of interest at baseline. The outcome is self-reported and there is no external validation. |
| | Probably No | / |
| | Definitely No | The authors have made no effort to exclude participants with the outcome of interest at baseline. |

| | | |
|---|---|---|
| Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Definitely Yes | The study adjusts at a minimum for 1) age, 2) sex, 3) smoking at least one measure of 4) socioeconomic status such as level of income or education or occupation, 5) family history, 6) alcohol consumption, 7) weight or BMI and 8) physical activity in the analysis. |
| | Probably Yes | Adjusts at a minimum for age, sex, smoking, family history, and weight or BMI. |
| | Probably No | Adjusts at a minimum for age, sex, and smoking. |
| | Definitely No | The study does not adjust for any prognostic variables relevant to the outcome or does not adjust for age, sex. |
| Can we be confident in the assessment of the presence or absence of prognostic factors? | Definitely Yes | Typically, prognostic factors are self-reported by participants. This is considered acceptable. |
| | Probably Yes | / |
| | Probably No | Some studies may make assumptions regarding various prognostic factors. For example, a study may assume that all participants who did not answer the question on diabetes disease at baseline did not have diabetes. |
| | Definitely No | / |
| Can we be confident in the assessment of outcome? | Definitely Yes | All-cause mortality based on a government registry (e.g., National Death Index) with or without review by study physician or study staff.<br>National or local registries (e.g., National Program of Cancer Registries (NPCR)) with review by a study physician or study staff.<br>Medical records reviewed by a study physician or study staff. |
| | Probably Yes | / |
| | Probably No | Medical records without review by study physician or study staff. |
| | Definitely No | Report with no external validation. |
| Was the follow-up of cohorts adequate? | Definitely Yes | At least 90% retention for the duration of the study. |
| | Probably Yes | 80 to 89% retention for the duration of the study with loss to follow-up unlikely to be related to outcomes. |
| | Probably No | 80 to 89% retention for the duration of the study with loss to follow-up likely to be related to outcomes. |
| | Definitely No | Less than 80% follow-up. |

NOTE: the criterion of guidance for assessment of risk of bias was cite from *Zeraatkar D, Han MA, Guyatt GH, et al. Red and Processed Meat Consumption and Risk for All-Cause Mortality and Cardiometabolic Outcomes: A Systematic Review and Meta-analysis of Cohort Studies. Ann Intern Med. 2019 19; 171(10):703-710. doi: 10.7326/M19-0655.*

**Supplementary Table 4.** Result of risk of bias assessment (cohort study)

| Author year | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Funding source |
|---|---|---|---|---|---|---|---|---|
| Xie 2021 | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably no | Not report |
| Nakajima 2021 | Definitely no | Definitely yes | Definitely yes | Definitely no | Definitely yes | Definitely yes | Probably yes | Definitely yes |
| Todisco 2020 | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Not report | Definitely yes |
| Hung 2017 | Definitely yes | Definitely yes | Definitely yes | Definitely no | Definitely yes | Definitely yes | Not report | Definitely yes |
| Miyajima 2016 | Definitely yes | Definitely yes | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely yes | Not report |
| McGovern 2014 | Definitely yes | Definitely yes | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely yes | Not report |
| Razay 2009 | Definitely yes | Definitely yes | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely yes | Not report |

**Supplementary Table 5.** Detailed guidance for assessment of risk bias (RCT)

| Item | Instruction | |
|---|---|---|
| Was the allocation sequence adequately generated? | Definitely Yes | Trials that assign participants to alternative interventions using a randomly generated sequence.<br>Examples of methods for developing a randomly generated allocation sequence include a random number generator, random number table, coin tossing, shuffling cards or envelopes, and throwing dice. If a trial is described as 'randomized' without any additional details related to how the allocation sequence was developed, we will assume that the allocation sequence was appropriately developed.<br>*Minimization may be implemented without a random element, and this is considered to be equivalent to being random. |
| | Probably Yes | / |
| | Probably No | A simple statement such as 'we randomly allocated' or 'using a randomized design' is often insufficient to be confident that the allocation sequence was genuinely randomized. |
| | Definitely No | The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:<br>• Sequence generated by odd or even date of birth;<br>• Sequence generated by some rule based on date (or day) of admission;<br>• Sequence generated by some rule based on hospital or clinic record number.<br>Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:<br>• Allocation by judgement of the clinician;<br>• Allocation by preference of the participant;<br>• Allocation based on the results of a laboratory technician. |
| Was the allocation adequately concealed? | Definitely Yes | Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:<br>• Central allocation (including telephone, web-based, and pharmacy-controlled, randomization);<br>• Sequentially numbered drug containers of identical appearance;<br>• Sequentially numbered, opaque, sealed envelopes. |
| | Probably Yes | Trials in which healthcare providers were blind to the intervention but which provide no information on allocation concealment and in which there are no major baseline imbalances. |
| | Probably No | Insufficient information to permit judgement of risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement. |
| | Definitely No | Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:<br>• Using an open random allocation schedule (e.g. a list of random numbers);<br>• Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);<br>• Alternation or rotation;<br>• Date of birth;<br>• Case record number;<br>• Any other explicitly unconcealed procedure. |

| | | |
|---|---|---|
| Blinding of participants | Definitely Yes | Any one of the following:<br>• No blinding or incomplete blinding of participants and personnel, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;<br>• Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;<br>• If it is described as “double-blind”, or “double-dummy”;<br>• Explicit statement that a group of interest was blinded → LOW risk of bias for that group;<br>• Explicit statement investigators were blinded → LOW risk of bias for study personnel. |
| | Probably Yes | / |
| | Probably No | • Insufficient information to permit judgment;<br>• Therapy trials in which healthcare providers are described as being blind to the intervention but allocation concealment was inadequate. |
| | Definitely No | Any one of the following:<br>• No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;<br>• Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;<br>• Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias;<br>• Explicit statement that a group of interest was not blinded;<br>• Explicit description of the trial as “open label” or “unblinded”, or “single blinded”.<br>Please note, if the outcome is an objective outcome (e.g., PSG outcomes), the risk of bias will generally be of less concern. |
| Blinding of healthcare providers | Definitely Yes | Any one of the following:<br>• No blinding or incomplete blinding of participants and personnel, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;<br>• Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;<br>• If it is described as “double-blind”, or “double-dummy”;<br>• Explicit statement that a group of interest was blinded → LOW risk of bias for that group;<br>• Explicit statement investigators were blinded → LOW risk of bias for study personnel. |
| | Probably Yes | / |
| | Probably No | • Insufficient information to permit judgment;<br>• Therapy trials in which healthcare providers are described as being blind to the intervention but allocation concealment was inadequate. |
| | Definitely No | Any one of the following:<br>• No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;<br>• Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;<br>• Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias;<br>• Explicit statement that a group of interest was not blinded;<br>• Explicit description of the trial as “open label” or “unblinded”, or “single blinded”.<br>Please note, if the outcome is an objective outcome (e.g., PSG outcomes), the risk of bias will generally be of less concern. |

| | | |
|---|---|---|
| Blinding of data collectors | Definitely Yes | - No blinding but the review authors judge that the outcome and the outcome measurement are not likely influenced by lack of blinding.<br>If the outcome is objective (e.g., mortality), lack of blinding is "probably low risk" but check for objective verification/measurement of the outcome.<br>Blinding of participants and key study personnel ensured, and unlikely that blinding could have been broken.<br>- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the nonblinding of others unlikely to introduce bias. |
| | Probably Yes | / |
| | Probably No | / |
| | Definitely No | No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.<br>- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.<br>- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias. |
| Blinding of outcome assessors | Definitely Yes | Any one of the following:<br>• No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;<br>• Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.<br>Explicit statement investigators were blinded → LOW risk of bias for outcome assessors.<br>No explicit statement about blinding status of either patients, health care providers, data collectors, or outcome adjudicators, and:<br>• Placebo controlled drug trial → LOW risk of bias for those groups;<br>• Active control drug trial (A vs. B) and mention of "double -dummy" or that medications were identical or matched → LOW risk of bias for those groups. |
| | Probably Yes | / |
| | Probably No | Any one of the following:<br>• Insufficient information to permit judgment;<br>No explicit statement about blinding status of either patients, health care providers, data collectors, or outcome adjudicators, and:<br>• Active control drug trial (A vs. B) but no mention of "double-dummy" or that medications were identical or matched. |
| | Definitely No | Any one of the following:<br>• No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;<br>• Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.<br>Explicit statement that a group of interest was not blinded<br>Explicit description of the trial as "open label" or "unblinded". |

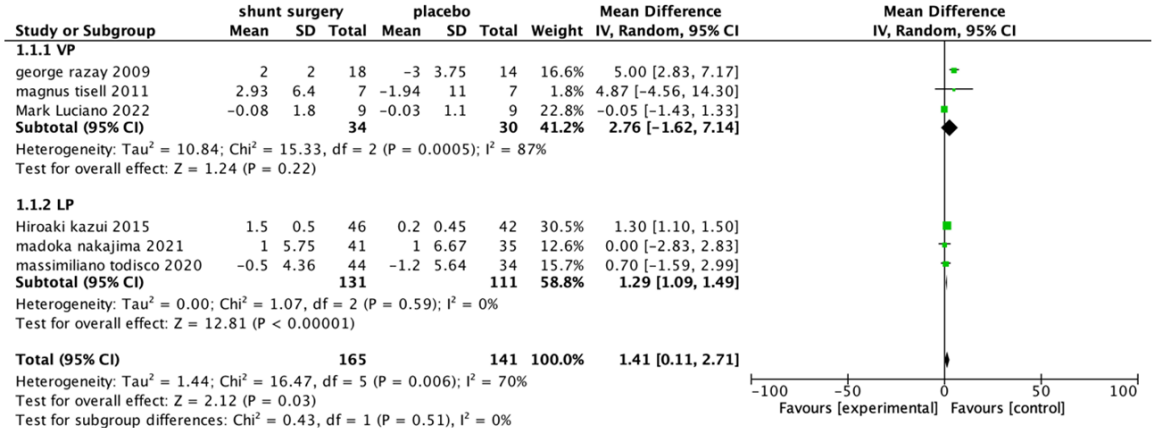
| | | |
|---|---|---|
| Blinding of data analysts | Definitely Yes | No blinding but the review authors judge that the outcome and the outcome measurement are not likely influenced by lack of blinding<br>Blinding of participants and key study personnel ensured, and unlikely that blinding could have been broken.<br>Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the nonblinding of others unlikely to introduce bias. |
| | Probably Yes | / |
| | Probably No | / |
| | Definitely No | No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.<br>For diet studies that are not amenable to placebo control, analyst's/ biostatiscian's are one of the few study personnel that can be blinded, please rate as "probably high risk of bias".<br>- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.<br>- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias. |
| Was loss to follow-up (missing outcome data) infrequent? | Definitely Yes | Trials in which missing outcome data (including outcome data that has been imputed) <10%. |
| | Probably Yes | Trials in which missing outcome data (including outcome data that has been imputed) is between 10% to 15% and missing outcome data is unlikely to be related to the true outcome and there is no imbalance in numbers of or reasons for missing data across intervention groups. |
| | Probably No | Trials in which missing outcome data (including outcome data that has been imputed) is between 10% to 15% and missing outcome data is likely to be related to the true outcome or there are imbalances in numbers of or reasons for missing data across intervention groups. |
| | Definitely No | Trials in which missing outcome data (including outcome data that has been imputed) >15%. |
| Are reports of the study free of selective outcome reporting? | Definitely Yes | Results for outcomes that were analyzed and reported according to a pre-specified statistical analysis plan or protocol (including the timepoint for the measurement of the outcome). |
| | Probably Yes | Results for outcomes that were analyzed and reported but that were not prespecified in a statistical analysis plan or protocol but the timepoint at which results are reported is consistent with the timepoint for other outcomes in the trial report or there is little reason to believe the outcome was selectively reported.<br>Please note that outcomes that were not prespecified in a protocol or statistical analysis plan and that are reported in the trial preprint or publication should be rated at probably low risk of bias unless there are other important reasons to suspect that results for those outcomes were selectively reported (e.g., results are presented at timepoints that don't match the timepoints reported for other outcomes). |
| | Probably No | Results for outcomes that were analyzed and reported but that were not prespecified in a statistical analysis plan or protocol but the timepoint at which results are reported is not consistent with the timepoint for other outcomes in the trial report or there are other reasons to believe that the outcome is selectively reported. |
| | Definitely No | Results for outcomes that were analyzed and reported for which there are inconsistencies with the statistical analysis plan or protocol. These inconsistencies may include outcome measures of interest or the timepoints for the measurement of outcomes. |

**Supplementary Table 6.** Result of risk bias assessment (RCT)

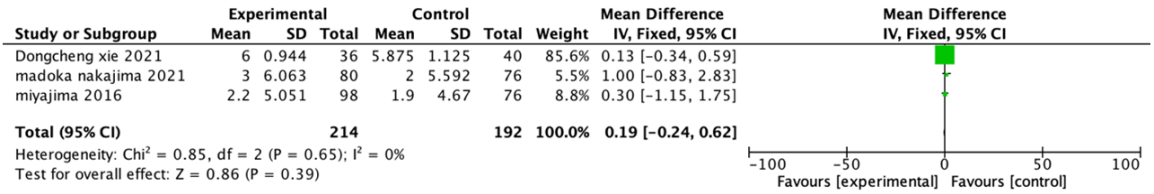
| Author year | Allocation sequence generated | Allocation concealment | Blinding of participants | Blinding of healthcare providers | Blinding of data collectors | Blinding of outcome assessors or adjudicators | Blinding of data analysts | Incomplete outcome data | Selective outcome reporting |
|---|---|---|---|---|---|---|---|---|---|
| Luciano 2022 | Definitely low | Definitely low | Definitely low | Probably high | Probably high | Probably high | Probably high | Definitely low | Probably high |
| Kazui [1] 2015 | Definitely low | Definitely low | Definitely high | Probably low | Probably low | Definitely high | Probably low | Probably low | Probably low |
| Goms 2012 | Definitely low | Definitely low | Definitely low | Definitely high | Probably high | Probably high | Probably high | Definitely low | Probably high |
| Tisell 2011 | Probably high | Probably high | Definitely low | Definitely high | Definitely low | Definitely low | Probably high | Definitely low | Probably high |

**Supplementary Table 7.** Summary results of clinical change according to study type

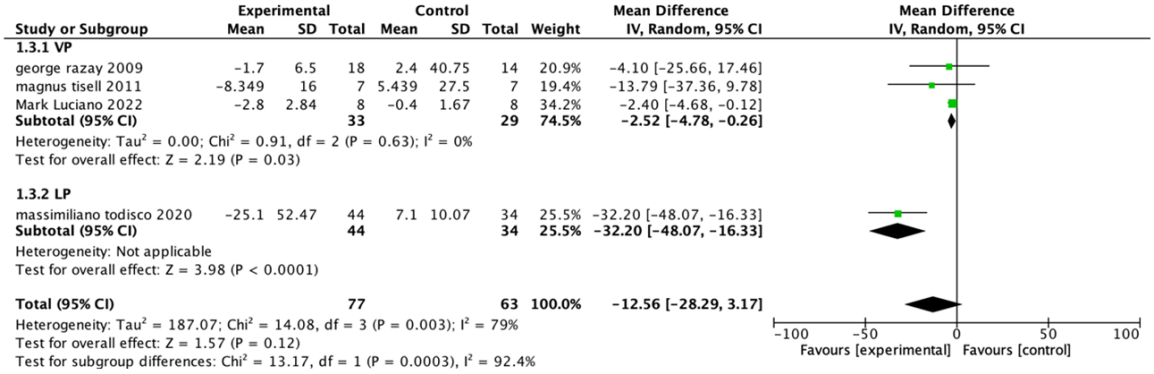
| | | RCT group | | | COHORT group | | |
|---|---|---|---|---|---|---|---|
| | | MD | 95% CI | $I^2$ | MD | 95% CI | $I^2$ |
| Cognitive improvement | Shunt vs. placebo | 0.89 | -0.27 to 2.05 | 52 | 1.97 | -1.20 to 5.15 | 81 |
| | VP vs. placebo | 0.11 | -1.60 to 1.81 | 2 | 5 | 2.83 to 7.13 | - |
| | LP vs. placebo | 1.30 | 1.10 to 1.50 | - | 0.42 | -1.36 to 2.20 | 0 |
| 10m walks | Shunt vs. placebo | -2.51 | -4.78 to -0.23 | 0 | -19.14 | -46.21 to 8.33 | 76 |
| | VP vs. placebo | -2.52 | -4.78 to -0.23 | 0 | -4.10 | -25.66 to 17.46 | - |
| | LP vs. placebo | - | - | - | -32.20 | -48.07 to -16.33 | 76 |
| Urinary symptoms | LP vs. placebo | -0.23 | -0.33 to -0.13 | - | -0.70 | -1.14 to -0.26 | - |



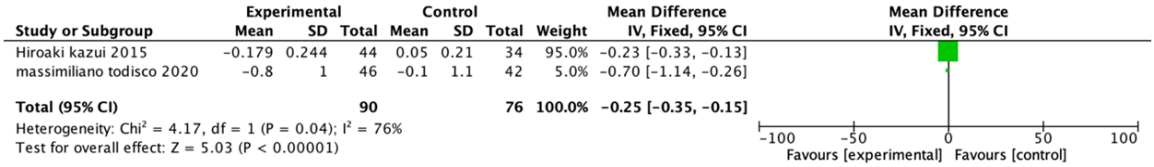

**Supplementary Figure 1.** Result of cognitive change between shunt surgery and placebo in a random model.



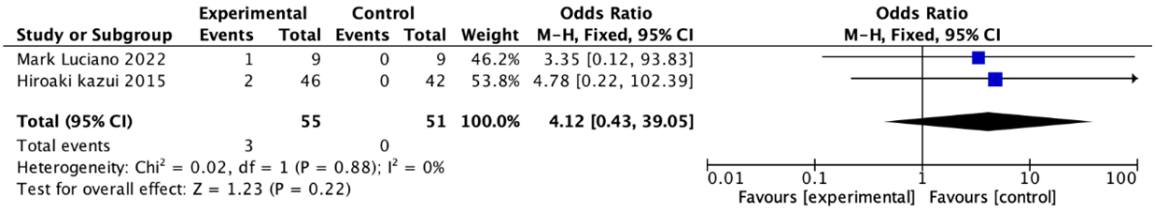

**Supplementary Figure 2.** Result of cognitive change between VP and LP in a fixed model.



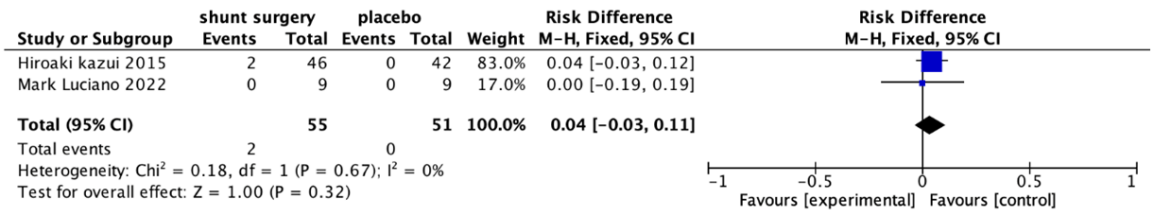

**Supplementary Figure 3.** Results of gait improvement between shunt surgery and placebo.



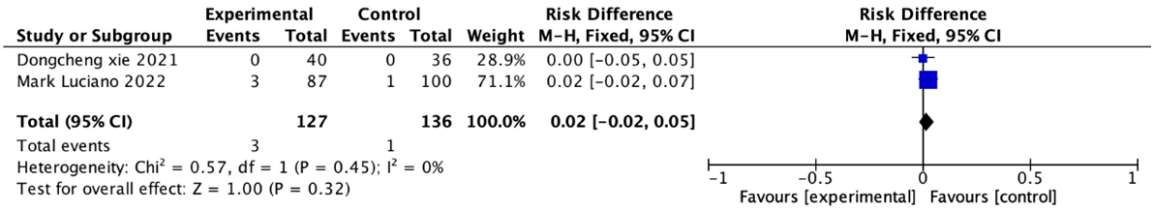

**Supplementary Figure 4.** Results of urinary symptom improvement between LP and placebo.



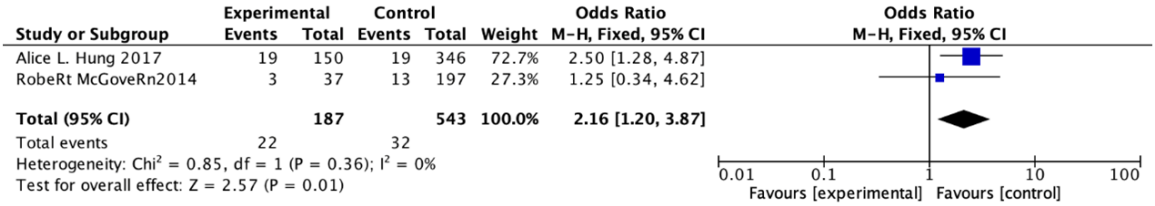

**Supplementary Figure 5.** Results of subdural hematoma occurrence between shunt surgery and placebo.



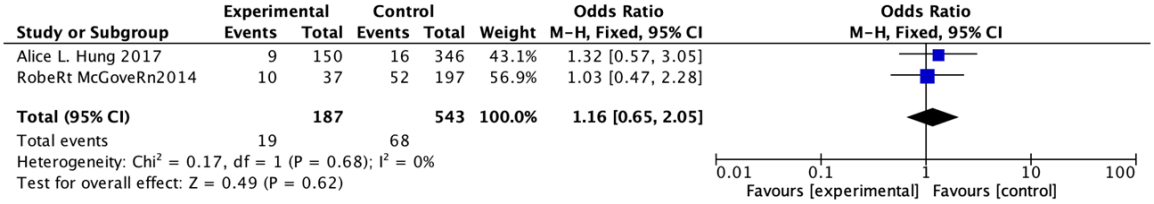

**Supplementary Figure 6.** Results of subdural hematoma needing surgery between shunt surgery and placebo.



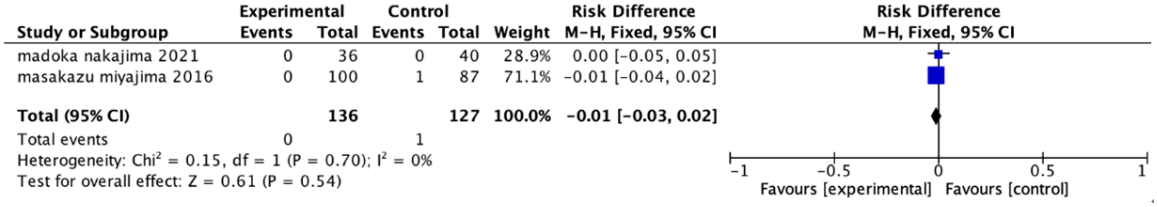

**Supplementary Figure 7.** Results of subdural hematoma between LP and VP.



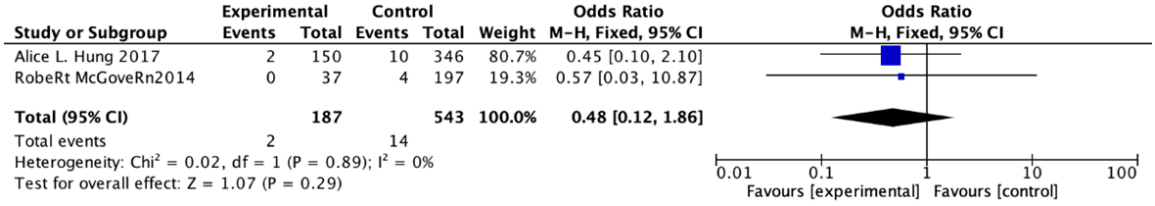

**Supplementary Figure 8.** Results of subdural hematoma between VA and VP.



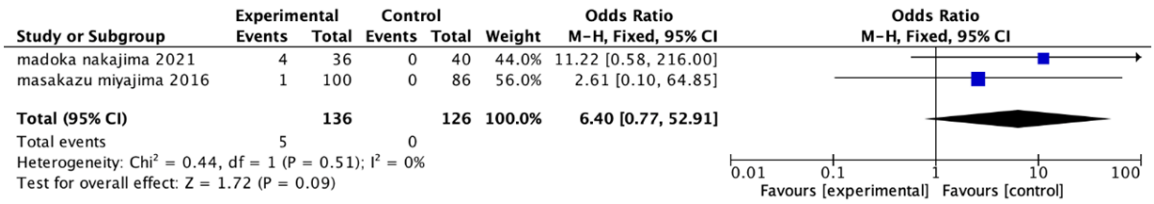

**Supplementary Figure 9.** Results of subdural hygroma between VA and VP.



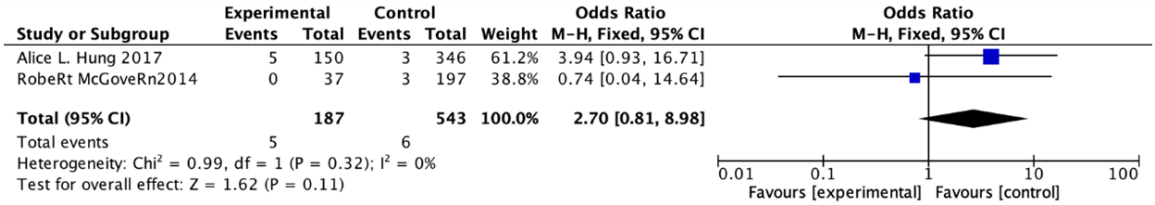

**Supplementary Figure 10.** Results of the occurrence rates of infection between VP and LP.



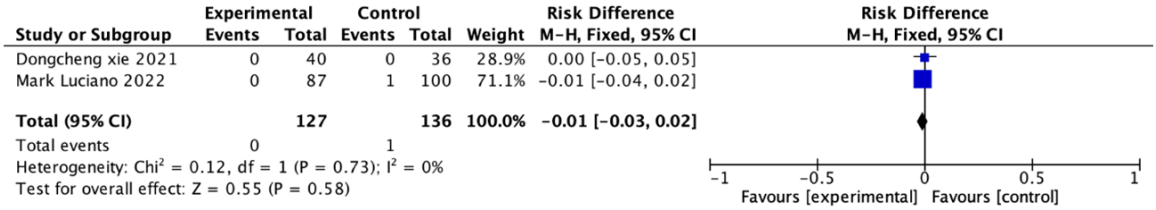

**Supplementary Figure 11.** Results of the occurrence rates of infection between VA and VP.



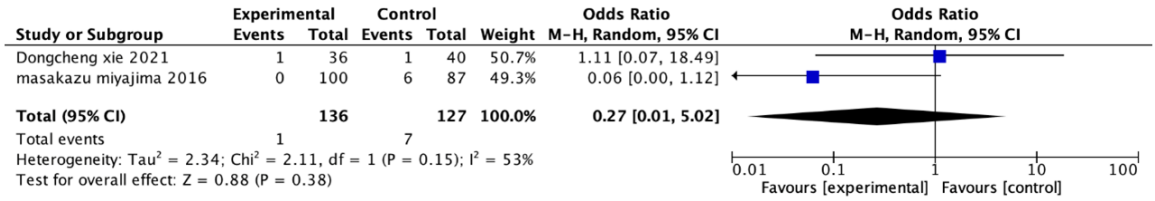

**Supplementary Figure 12.** Results of occurrence rates of hemorrhage between LP and VP.



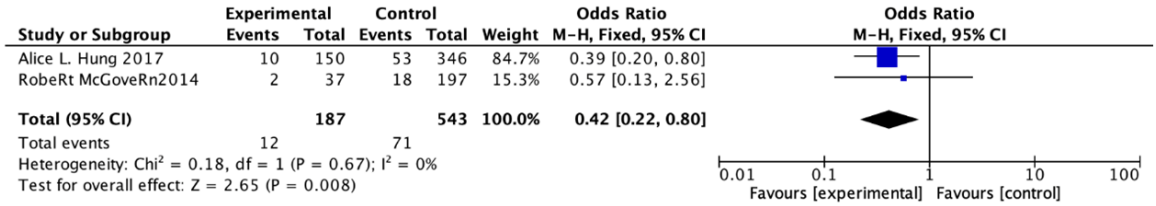

**Supplementary Figure 13.** Results of the occurrence rates of hemorrhage between VA and VP.



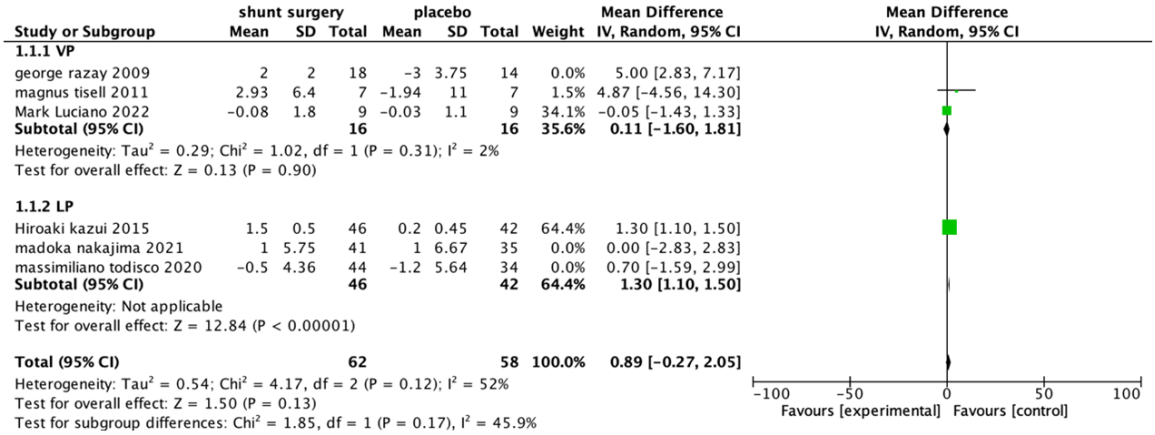

**Supplementary Figure 14.** Results of the occurrence rates of tube blockage between LP and VP.



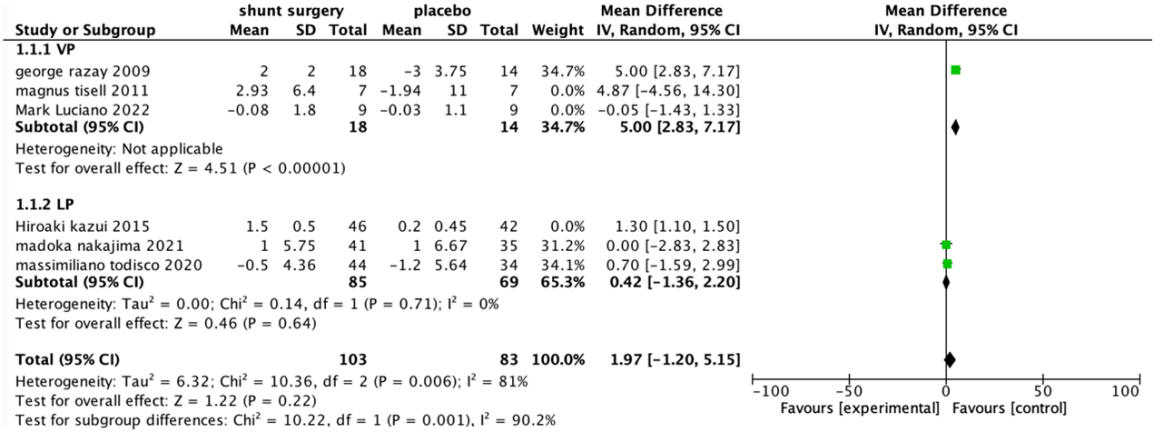

**Supplementary Figure 15.** Results of the occurrence rates of tube revision between LP and VP.



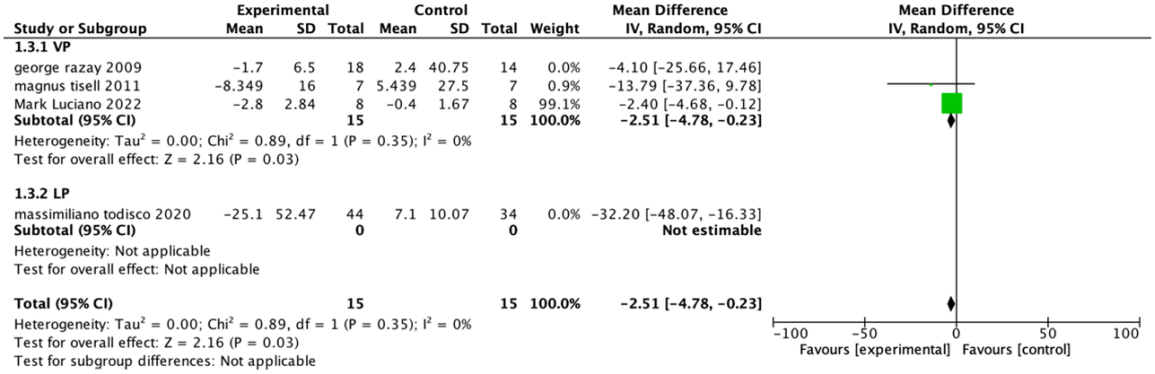

**Supplementary Figure 16.** Results of the occurrence rates of tube revision between VA and VP.



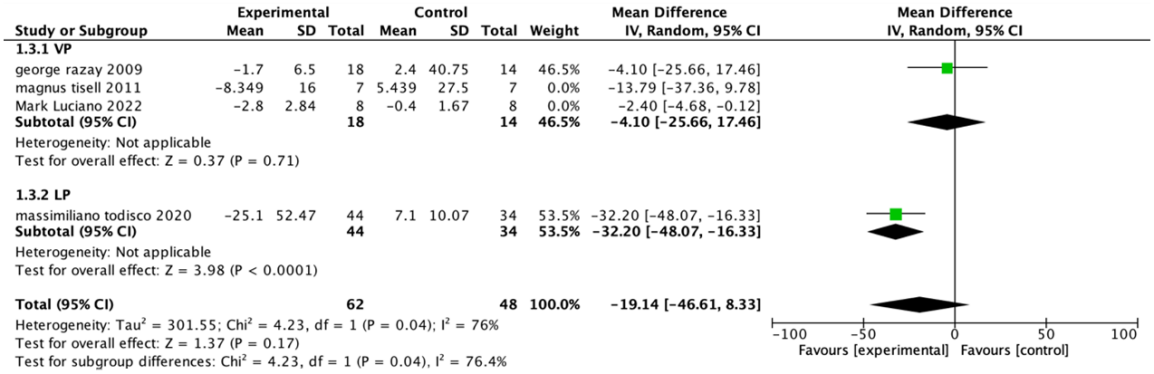

**Supplementary Figure 17.** Results of MMSE improvement between shunt surgery and placebo in the RCT group.



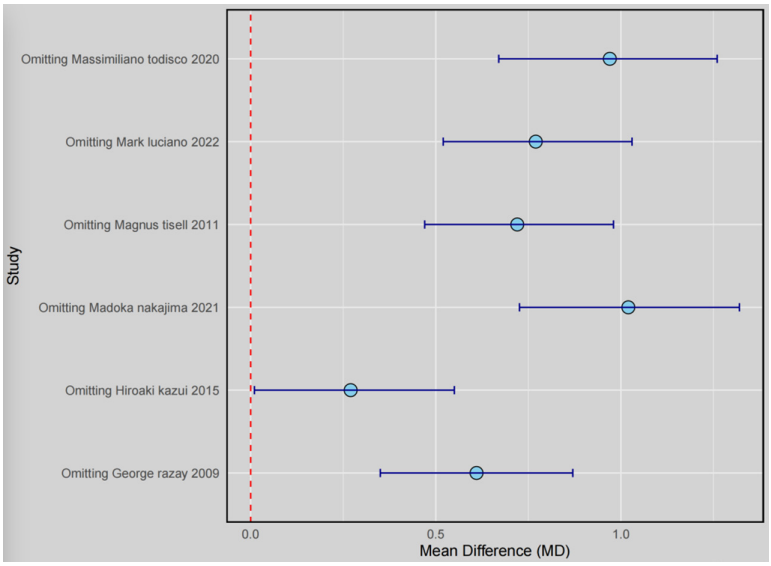

**Supplementary Figure 18.** Results of MMSE improvement between shunt surgery and placebo in the cohort study group.



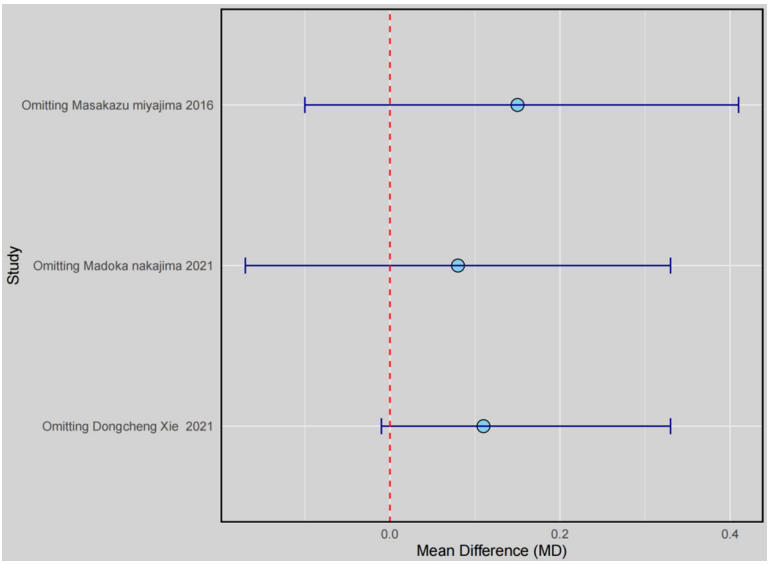

**Supplementary Figure 19.** Results of 10m walk changes between shunt surgery and placebo in the RCT group.



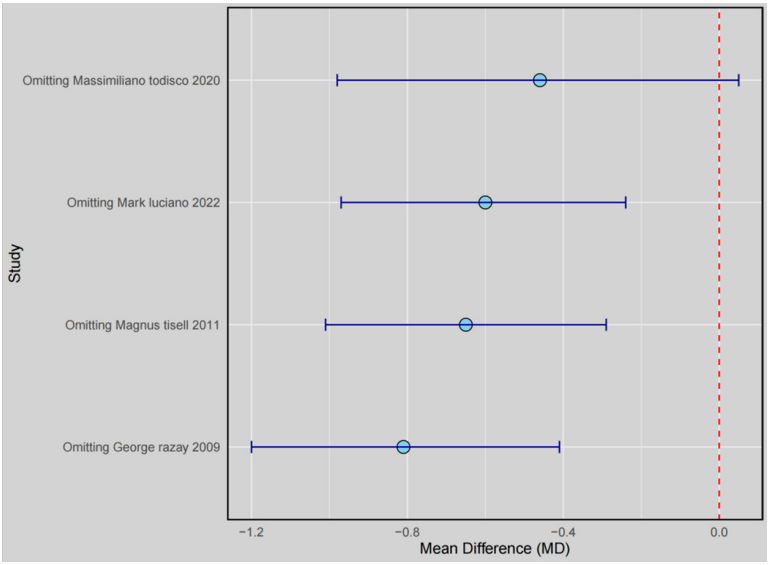

**Supplementary Figure 20.** Results of 10m walk changes between shunt surgery and placebo in the cohort group.




**Supplementary Figure 21.** Sensitivity analysis of studies reporting the effect of cognitive improvement between shunt surgery and placebo.




**Supplementary Figure 22.** Sensitivity analysis of studies reporting the effect of cognitive improvement between VP and LP.




**Supplementary Figure 23.** Sensitivity analysis of studies reporting the effect of 10m walk changes between shunt surgery and placebo.

**Appendix 1.** The lists of studies excluded in full-text screen

## References


[1] Williams MA, Nagel SJ, Golomb J, Jensen H, Dasher NA, Holubkov R, Edwards RJ, Luciano MG, Zwimpfer TJ, Katzen H, Moghekar A, Wisoff JH, McKhann GM and Hamilton MG. Safety and effectiveness of the assessment and treatment of idiopathic normal pressure hydrocephalus in the adult hydrocephalus clinical research network. J Neurosurg 2022; 137: 1289-1301.

[2] Tans JT and Boon AJ. How to select patients with normal pressure hydrocephalus for shunting. Acta Neurochir Suppl 2002; 81: 3-5.

[3] Segura-Hernández A, Hakim F, Ramón JF, Jiménez-Hakim E, Mejía-Cordovez JA, Quintero-Rueda D, Araque-Puello Y, Pedraza-Ciro C, Leal-Isaza JP, Mendoza-Mantilla J, Robles V, Gonzalez M, Jaramillo-Velásquez D and Gómez DF. Ventriculo-atrial shunt. Comparison of an ultrasound-guided peel-away technique versus conventional technique in the management of normal pressure hydrocephalus: a retrospective cohort. Surg Neurol Int 2021; 12: 531.

[4] Sand T, Bovim G, Grimse R, Myhr G, Helde G and Cappelen J. Idiopathic normal pressure hydrocephalus: the CSF tap-test may predict the clinical response to shunting. Acta Neurol Scand 1994; 89: 311-316.

[5] Rydja J, Kollén L, Ulander M, Tullberg M and Lundin F. Physical capacity and activity in patients with idiopathic normal pressure hydrocephalus. Front Neurol 2022; 13: 845976.

[6] Paidakakos N, Borgarello S and Naddeo M. Indications for endoscopic third ventriculostomy in normal pressure hydrocephalus. Acta Neurochir Suppl 2012; 113: 123-127.

[7] Lemcke J, Meier U, Müller C, Fritsch MJ, Kehler U, Langer N, Kiefer M, Eymann R, Schuhmann MU, Speil A, Weber F, Remenez V, Rohde V, Ludwig HC and Stengel D. Safety and efficacy of gravitational shunt valves in patients with idiopathic normal pressure hydrocephalus: a pragmatic, randomised, open label, multicentre trial (SVASONA). J Neurol Neurosurg Psychiatry 2013; 84: 850-857.

[8] Larsson J, Israelsson H, Eklund A, Lundin-Olsson L and Malm J. Falls and fear of falling in shunted idiopathic normal pressure hydrocephalus-the idiopathic normal pressure hydrocephalus comorbidity and risk factors associated with hydrocephalus study. Neurosurgery 2021; 89: 122-128.

[9] Lalou AD, Czosnyka M, Garnett MR, Nabbanja E, Petrella G, Hutchinson PJ, Pickard JD and Czosnyka Z. Shunt infusion studies: impact on patient outcome, including health economics. Acta Neurochir (Wien) 2020; 162: 1019-1031.

[10] Hülser M, Spielmann H, Oertel J and Sippl C. Motor skills, cognitive impairment, and quality of life in normal pressure hydrocephalus: early effects of shunt placement. Acta Neurochir (Wien) 2022; 164: 1765-1775.

[11] Hellström P, Klinge P, Tans J and Wikkelsø C. The neuropsychology of iNPH: findings and evaluation of tests in the European multicentre study. Clin Neurol Neurosurg 2012; 114: 130-134.

[12] Hellström P, Edsbagge M, Blomsterwall E, Archer T, Tisell M, Tullberg M and Wikkelsø C. Neuropsychological effects of shunt treatment in idiopathic normal pressure hydrocephalus. Neurosurgery 2008; 63: 527-535; discussion 535-526.

[13] Dias SF, Graf C, Jehli E, Oertel MF, Mahler J, Schmid Daners M and Stieglitz LH. Gait pattern analysis in the home environment as a key factor for the reliable assessment of shunt responsiveness in patients with idiopathic normal pressure hydrocephalus. Front Neurol 2023; 14: 1126298.

[14] Bäcklund T, Frankel J, Israelsson H, Malm J and Sundström N. Trunk sway in idiopathic normal pressure hydrocephalus-quantitative assessment in clinical practice. Gait Posture 2017; 54: 62-70.

[15] Andrén K, Wikkelsø C, Sundström N, Israelsson H, Agerskov S, Laurell K, Hellström P and Tullberg M. Survival in treated idiopathic normal pressure hydrocephalus. J Neurol 2020; 267: 640-648.

[16] Al-Zain FT, Rademacher G, Meier U, Mutze S and Lemcke J. The role of cerebrospinal fluid flow study using phase contrast MR imaging in diagnosing idiopathic normal pressure hydrocephalus. Acta Neurochir Suppl 2008; 102: 119-123.