Archives of Gerontology and Geriatrics 87 (2020) 103977

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

# Postoperative delirium after hip surgery is a potential risk factor for incident dementia: A systematic review and meta-analysis of prospective studies

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ARTICLE INFO

*Keywords:*
Hip fractures
Hip replacement
Dementia
Delirium
Meta-analysis

ABSTRACT

*Background:* Although a few trials have explored the relationship between postoperative delirium (POD) and incident dementia in patients with hip surgery, the numbers of participants in each study are relatively small. Thus, we performed a meta-analysis to examine whether POD after hip surgery is a risk factor for incident dementia.

*Methods:* Six prospective cohort studies investigating the development of incident dementia in patients with POD after hip surgery were retrieved from PubMed, Embase, and the Cochrane Library. We performed a pairwise meta-analysis using fixed- and random- effect models.

*Results:* POD significantly increased the risk of incident dementia and cognitive decline (overall odds ratio [ORs] = 8.957; 95 % confidence interval [CI], 5.444–14.737; $P < 0.001$ in fixed-effects model; overall ORs = 8.962; 95 % CI, 5.344–15.029; $P < 0.001$ in random-effects model). A publication bias was not evident in this study.

*Conclusions:* Our meta-analysis revealed that POD after hip surgery is a risk factor for incident dementia. Early identification of cognitive function should be needed after surgery and appropriate prevention and treatment for dementia will be required, especially in cases with POD.

## 1. Introduction

Delirium is a neuropsychiatric syndrome with a decompensation of cerebral function (Rudolph et al., 2008) and is characterized by an acute disturbance in attention and cognitive functions with an abrupt onset (Association, 2013). Although delirium is uncommon among community-dwelling elderly, it is a very common complication among hospitalized elderly patients (Siddiqi, House, & Holmes, 2006). Both predisposing factors, including cognitive dysfunction, dementia, and underlying comorbidity, and precipitating events (including major trauma and anesthesia) play an important role in the occurrence of delirium (Fong, Davis, Growdon, Albuquerque, & Inouye, 2015, Fong, Hshieh et al., 2015; Inouye, 1999). Delirium is usually temporary and reversible, and delirious patients might have fluctuating clinical courses (Inouye, Westendorp, & Saczynski, 2014; Oldham, Flanagan, Khan, Boukrina, & Marcantonio, 2018). Delirium increases morbidity and length of hospital stay, thus reducing the compliance of patients to the treatment for the medical condition (Minden et al., 2005). Finally, it might increase re-hospitalization and mortality rates in the long term (Liu, Wang, & Xiao, 2018; Minden et al., 2005).

Hip surgery is frequently performed for elderly patients with a hip fracture or degenerative arthritis. Elderly patients undergoing hip surgery are at a risk of incident delirium (Bruce, Ritchie, Blizard, Lai, & Raven, 2007). Approximately 20–50 % of patients experience delirium after hip surgery (Bruce et al., 2007). Old age, comorbidity, bleeding during operation, anesthesia, and admission to the intensive care unit after hip surgery might be risk factors for postoperative delirium (POD) (Dovjak et al., 2013), which is a risk factor for decreased functional outcome after surgery, prolonged length of hospital stay, and mortality (Mitchell, Harvey, Brodaty, Draper, & Close, 2017; Vochteloo et al., 2013).

Preoperative dementia and cognitive dysfunction are well-known risk factors for POD (Oh et al., 2015). Likewise, delirium in patients without previous dementia induces incident dementia or cognitive

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https://doi.org/10.1016/j.archger.2019.103977
Received 8 September 2019; Received in revised form 7 November 2019; Accepted 7 November 2019
Available online 11 November 2019
0167-4943/ 

dysfunction (Lundstrom, Edlund, Bucht, Karlsson, & Gustafson, 2003; Witlox et al., 2010). Several studies have reported the relationship between POD and incident dementia in patients undergoing hip surgery (Bickel, Gradinger, Kochs, & Forstl, 2008; Kat et al., 2008; Krogseth, Wyller, Engedal, & Juliebo, 2011; Lundstrom et al., 2003; Olofsson et al., 2018). However, the numbers of participants in each study are relatively small. To the best of our knowledge, no meta-analysis has assessed the relationship between POD and incident dementia after hip surgery. Thus, in this study, we aimed to investigate whether POD after hip surgery in patients without preoperative dementia would increase the risk of incident dementia by meta-analysis.

## 2. Methods

### 2.1. Search methods for identifying studies

This meta-analysis was conducted in line with the updated Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines (Shamseer et al., 2015). PubMed-Medline, Embase, and Cochrane Library searches were performed in August 13th, 2019, using the following key terms: (Hip fractures OR femoral Neck Fractures OR femur intertrochanteric fracture OR hip replacement OR hip arthroplasty OR hip surgery OR hip operation) AND (delirium OR confusion OR inattentiveness OR disorientation OR agitation) AND (Dementia OR cognitive impairment OR cognitive decline OR Alzheimer Disease). An overview of the search strategy is presented in Supplementary Appendix A. We included all prospective cohort studies investigating the development of incident dementia in patients with hip surgery including hip fracture and elective hip arthroplasty. We imposed no language restriction. We also searched for unpublished and grey literature using the databases/trial registries: World Health Organization Clinical Trial Register, EU clinical trials register, ClinicalTrials.gov, and OpenGrey.

### 2.2. Study selection criteria

The identified records were saved to EndNote software (X7.2; Thomson Reuters). Two independent reviewers (SYL, SJL) first screened all titles and abstracts to identify relevant investigations. Inclusion criteria were (1) articles reporting a prospective cohort study with at least 6 months follow-up that (2) described the development of incident dementia in patients with hip surgery. There were no limitations in surgical procedure. Studies where a validated diagnostic screening tool has not been used to define dementia at baseline (e.g. pre-operatively) were excluded. Reviews, basic science articles, comments, letters, and protocols were also excluded. When updates of earlier studies were identified, we used only the latest updates. We employed the Newcastle-Ottawa Scale (Stang, 2010) to assess the quality of the selected studies, the assessment covers the selection of study groups, comparability of study groups, outcomes assessment and follow-up.

### 2.3. Outcome measures, data extraction, and publication bias

The presence of POD was defined by diagnostic screening tools validated for use with elderly people, e.g. the Confusion Assessment Method (CAM) or Diagnostic and Statistical Manual of Mental Disorders (DSM) system (Smith et al., 2017). The assessment time of delirium after surgery included only articles measured within one week after surgery. The primary outcome of interest was the presence of incident dementia and cognitive decline diagnosed according to standardized criteria (such as the DSM system, International Classification of Diseases, California, mini-mental status examination, and NINDS-AIREN) (Sharp et al., 2011). For every eligible study, the following data were extracted and entered into a spreadsheet by the two reviewers (SYL, SJL): first author's family name, year of publication, number of patients, mean age at the time of hip surgery, assessment time and tools for delirium and dementia, and follow-up duration. We assessed the publication bias using Begg's funnel plot (Begg & Mazumdar, 1994) and Egger's test (Egger, Davey Smith, Schneider, & Minder, 1997).

### 2.4. Statistical analysis

Effect sizes were computed as odds ratios (ORs) and standardized mean differences (SMDs). To derive overall Hedges' g-pooled effect sizes, SMDs were converted to ORs. Heterogeneity among comparable studies was explored using the chi-squared ($\chi^2$) and $I^2$ tests. Values of $P > 0.1$ and $I^2 < 50$ % were considered statistically significant. While significant heterogeneity was not evident among the selected studies ($P = 0.379$ and $I^2 = 5.9$ %), we used both fixed- and random-effects models to quantify the pooled effect size of the included studies. All analyses were conducted with the aid of Comprehensive Meta-Analysis software (version 3.3; Biostat, Englewood, NJ, USA). The study did not require institutional review board approval because we did not personally enroll any human subjects.

## 3. Results

### 3.1. Description of included studies

The primary database search yielded 356 records. After duplicates were removed, the titles and abstracts of 231 articles were initially screened, and 16 selected for full-text review. The full texts were read, and 6 were considered relevant by qualitative analysis (Bickel et al., 2008; Kat et al., 2008; Krogseth et al., 2011; Lundstrom et al., 2003; Neerland et al., 2017; Olofsson et al., 2018). The studies selected for final inclusion (or exclusion) are shown in Fig. 1. The characteristics and quality assessments of the included studies are summarized in Tables 1 and 2, respectively. In terms of quantitative analysis, these six studies (published from 2003 to 2018) fulfilled our inclusion criteria. The studies identified for meta-analysis included 844 participants. Study sample sizes varied from 78 to 213. Follow-up duration ranged from 6 month to 5 years.

### 3.2. Results after analysis and publication bias

POD significantly increased the risk of incident dementia (overall ORs = 8.957; 95 % confidence interval [CI], 5.444–14.737; $P < 0.001$ in fixed-effect model; overall ORs = 8.962; 95 % CI, 5.344–15.029; $P < 0.001$ in random-effect model) (Fig. 2). A publication bias was not evident in this study; the Begg's funnel plot was symmetric (Fig. 3), and the *P*-value for bias was 0.975 (Egger's test; all 6 trials).

## 4. Discussion

The current meta-analysis showed that POD increased the risk of incident dementia after hip surgery. The overall OR was about 8.96 in both fixed- and random-effect models. Among 844 participants undergoing hip surgery, 265 patients had POD, and 101 patients with POD were diagnosed as having incident dementia. We only included prospective cohort studies with at least 6 months of follow-up that described the development of incident dementia in patients undergoing hip surgery. To our knowledge, this is the first meta-analysis to investigate the risk of incident dementia after POD in patients undergoing hip surgery.

Several studies suggested that delirium is an early manifestation of dementia (Gross et al., 2012; Lundstrom et al., 2003; Witlox et al., 2010). Delirium was also the first sign of subclinical dementia (Rahkonen, Luukkainen-Markkula, Paanila, Sivenius, & Sulkava, 2000). Delirium might unmask unrecognized dementia (Fong, Davis et al., 2015) and signal the underlying vulnerability of the brain with diminished cognitive reserve and increase the risk for later dementia. There are a few hypotheses on the development of dementia after

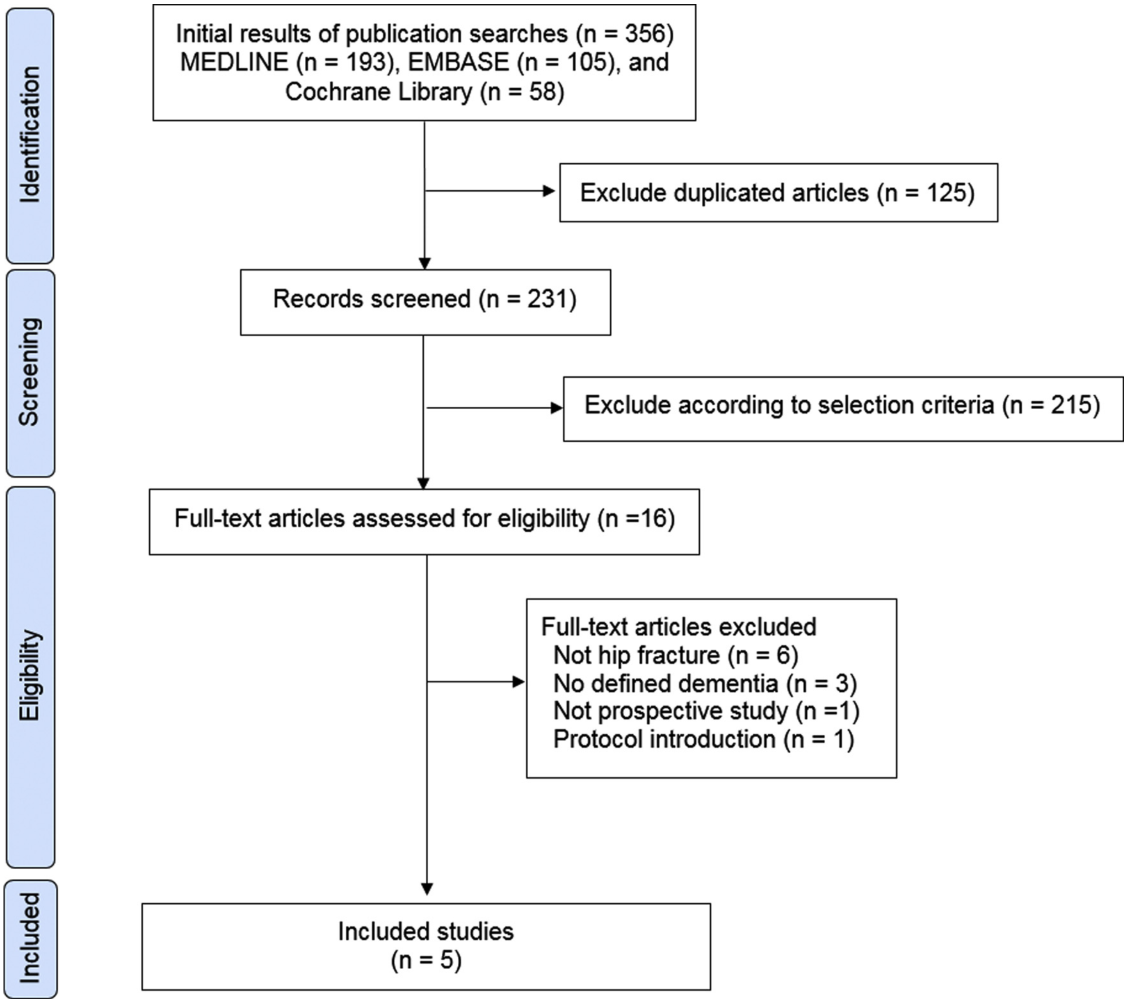


**Fig. 1.** A preferred reporting items for systematic review and meta-analysis flow diagram detailing the selection of clinical studies.

delirium. Precipitating conditions for POD in patients after hip surgery, including prolonged hypoxemia, anemia owing to major surgical bleeding, trauma from surgery or during hip fracture, and inflammation, can directly result in neural damage and lead to permanent cognitive impairment (Fong, Davis et al., 2015). Furthermore, deconditioning from the delirious state might lead to medical complications such as aspiration pneumonia, respiratory compromise, poor oral intake, and malnutrition, which may have toxic effects on brain function and lead to long-term cognitive dysfunction and dementia (Fong, Davis et al., 2015). Finally, antipsychotics or sedative medication for rescue from delirium might cause neural damage (Fong, Davis et al., 2015).

Six studies included in this meta-analysis revealed that POD is a risk factor for incident dementia after hip surgery without preoperative dementia. However, several risk factors cause incident dementia and POD. Lundstrom et al. revealed that preoperative decreased cognitive function and diabetes mellitus were independent risk factors of dementia (Lundstrom et al., 2003). Bickel et al. revealed that patients with incident dementia were older, had lower preoperative MMSE score, and longer durations of POD than patients without dementia (Bickel et al., 2008). Krogseth et al. demonstrated that dementia at 6 month after hip surgery was related with older age, higher heart rate on admission, mean arterial pressure (MAP) reduction during surgery, and higher American Society of Anesthesiology (ASA) score (Krogseth et al., 2011). Moreover, Neerland et al. demonstrated that old age, higher ASA score, use of vasopressor during surgery, and higher postoperative MAP were significant risk factor for incident dementia (Neerland et al., 2017).

Correction among modifiable precipitating risk factors is important for treating delirium (Hsieh, Ely, & Gong, 2013). Early detection of delirium and prompt initiation of treatment are keys for reducing the duration of delirium (Hsieh et al., 2013). Among previously mentioned risk factors, duration of delirium, intraoperative or postoperative MAP reduction, and use of intraoperative vasopressor are modifiable risk factors. Prolonged duration of delirium is related to mortality and functional recovery after hip fracture surgery (Bellelli et al., 2014; Zakriya, Sieber, Christmas, Wenz, & Franckowiak, 2004). Hence, care should be taken for early detection and treatment of delirium after hip surgery. In addition, MAP is important to maintain cerebral perfusion (Deckers et al., 2015; Walsh et al., 2013). MAP reduction during surgery increases the risk of acute kidney injury, myocardial injury, other cardiac complications, and dementia and incident delirium (Walsh et al., 2013). In addition, intraoperative use of vasopressor for treating MAP reduction might decrease cerebral tissue oxygen saturation (Meng et al., 2011). Moreover, hypertension is a well-known risk factor for dementia (Deckers et al., 2015). High sympathetic tone, stiffer blood vessel, and altered hemodynamic regulation related with hypertension might play an important role to vulnerability of cerebral perfusion in perioperative period (Iadecola & Davisson, 2008). Careful intraoperative and postoperative monitoring and management should be necessitated for preventing postoperative delirium and later development of dementia.

Regarding diabetes, there is controversy whether diabetes would increase the risk of incident dementia (Lundstrom et al., 2003; Olofsson et al., 2018). Some studies previously showed diabetes to be a positive risk factor for dementia in hip fracture patients or community-dwelling

**Table 1**
Characteristics of Included Individual Studies.

| Study | Region | N | Age of subjects | Gender of subjects (M:F) | Pre-fracture mental status | Ratios of emergent surgery | F/U period | Delirium assess tools | Delirium measure point | Dementia assess tools |
|---|---|---|---|---|---|---|---|---|---|---|
| Lundstrom et al. (2003) | Sweden | 78 | Aged 65 and older; Mean = 79.1 ± 8.1 (range 65–102) | 18:60 | No dementia assessed by means of interviews with relatives or caregivers | 100 % | 60 mo | DSM-IV | Postop. 8 hrs to 7 days | DSM-IV criteria |
| Bickel et al. (2008) | Germany | 200 | Aged 60 years and older; Mean = 73.8 ± 9.0 (range 60-97) | 62:138 | No dementia (by question) | 28 % | 38 mo | CAM | Postoperatively (no detail data) | 16 points or less on the 21-item T-MMSE |
| Kat et al. (2008) | Netherlands | 112 | Aged 70 years and older | 30:82 | No dementia | 42 % | Mean 30 mo | DSM-IV and CAM | Within 5 postop. days | DSM-IV criteria |
| Krogseth et al. (2011) | Norway | 106 | Aged 65 and older | 27:79 | No dementia | 100 % | 6 mo | CAM | Every weekday through the fifth postop. day or until discharge | DSM-IV criteria |
| Neerland et al. (2017) | Norway | 213 | Aged 65 and older | Not mentioned* | No dementia | 100 % | 12 mo | CAM | Every weekday through the fifth postop. day or until discharge | ICD-10 |
| Olofsson et al. (2018) | Sweden | 135 | Aged 70 and older | 34:101 | No dementia | 100 % | 36 mo | Modified Organic Brain Syndrome Scale, DSM-IV- | During hospitalization 3–5 days | DSM-IV-TR criteria |

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, CAM: Confusion Assessment Method, MMSE: Mini–Mental State Examination, ICD: The International Classification of Diseases.
* The female proportion of original population was 76 % while the final follow-up gender proportion was not mentioned.

**Table 2**
Newcastle-Ottawa Scale to Assess the Quality of the Selected Studies.

| Study | Representativeness of the exposed cohort | Selection of the non exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts | Total score |
|---|---|---|---|---|---|---|---|---|---|
| Lundstrom et al. (2003) | + | + | + | + | – | + | + | + | 7 |
| Bickel et al. (2008) | + | + | + | + | – | + | + | + | 7 |
| Kat et al. (2008) | + | + | + | + | – | + | + | + | 7 |
| Krogseth et al. (2011) | + | + | + | + | – | + | – | – | 5 |
| Neerland et al. (2017) | + | + | + | + | – | + | + | + | 7 |
| Olofsson et al. (2018) | + | + | + | + | – | + | + | + | 7 |

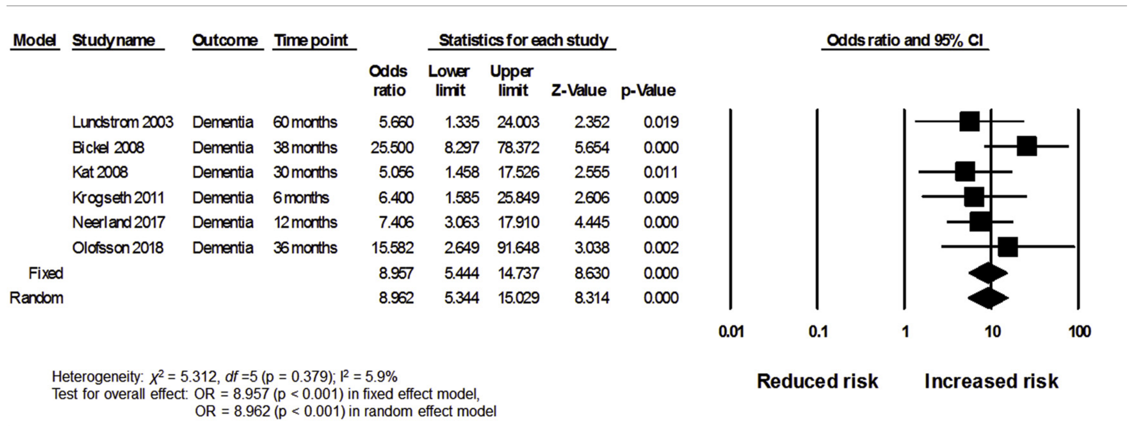


**Fig. 2.** Forest plot of the overall effect size of incident dementia by postoperative delirium after hip fracture. Effect sizes are indicated as odds ratios with 95 % confidence intervals.

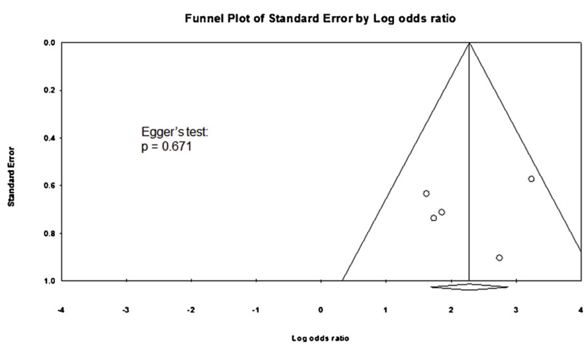


**Fig. 3.** Funnel plot.

patients (Lundstrom et al., 2003; Xu, Qiu, Winblad, & Fratiglioni, 2007). Diabetes is a well-known risk factor for vascular dementia owing to vascular endothelial injury by high glucose level (Xu et al., 2007). Furthermore, high blood glucose might be directly toxic to brain function (Xu et al., 2007). However, other studies failed to show that diabetes was a risk factor for dementia in the prospective community-based cohort study (Akomolafe et al., 2006). Notwithstanding, some studies suggested that diabetes has a protective effect of dementia. One study revealed that dementia patients with diabetes had a slower cognitive decline than those without diabetes (Dominguez, Marschoff, Gonzalez, Repetto, & Serra, 2012). The study by Olofsson et al., which was included in our meta-analysis, revealed that diabetes seemed to exert a protective effect against dementia (Olofsson et al., 2018). Insulin might play an important role in preventing oxidative stress in the progress of dementia (De Felice et al., 2009). Increases in insulin levels in patients with diabetes might have a protective role against the progression of brain damage by oxidative stress (Serra et al., 2009). Therefore, further studies would be needed to confirm the relationship between preoperative diabetes and incident dementia after hip surgery.

The current study had several limitations. First, heterogeneous methods to evaluate cognitive function or dementia were used in the included studies. However, both CAM and DSM-IV are well-adapted methods for diagnosing cognitive dysfunction or dementia (Fong, Davis et al., 2015). Moreover, the finding of an increased risk of dementia after POD are consistent, despite various methods for evaluation. Second, both elective and emergency hip surgeries were simultaneously included in this meta-analysis. The wide variation of ORs (5.056–25.500) of this study might result from the heterogeneity of surgical type. Among the included studies of this meta-analysis, four studies only included subjects with hip fractures (emergency operation) while the other two studies (Bickel et al., 2008; Kat et al., 2008) included participants after both elective and emergency hip surgeries. An emergency operation is a well-known risk factor for POD (Bruce et al., 2007), and hip fracture is one of the most common precipitating condition for delirium (Dovjak et al., 2013). However, Bickel's study, which has the lowest ratio (28 %) of subjects after emergency surgery, showed the highest OR (25.500) among the included studies, on the contrary of our anticipation.

Although our meta-analysis showed that POD after both elective and emergency hip surgeries increases the risk of incident dementia, further studies to identify the difference in risk of incident dementia after postoperative delirium between the two groups would be necessary. Third, incident dementia included both degenerative disease (Alzheimer) and vascular dementia in our meta-analysis. These two types of dementia had to be analyzed separately because of their differences in pathogenesis and prognosis. Finally, other confounding risk factors were not controlled in this study. As we mentioned above, there are numerous risk factors for delirium and dementia (Fong, Davis et al., 2015, Fong, Hshieh et al., 2015; Inouye, 1999). Thus, further studies to identify additional risk factors for incident dementia after hip surgery would be necessary.

In conclusion, our meta-analysis showed that POD after hip surgery is a risk factor for incident dementia. Early identification of cognitive function should be needed after surgery and appropriate prevention and treatment for dementia will be required, especially in cases with POD. Information about the risk of incident dementia has to be provided to patients with POD and caregivers.

## Declaration of Competing Interest

All authors declare no conflicts of interest.

## Acknowledgment

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2019R1C1C100632).

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.archger.2019.103977.

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