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## **New insights in the treatment of femoral neck fractures**

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### **Citation**

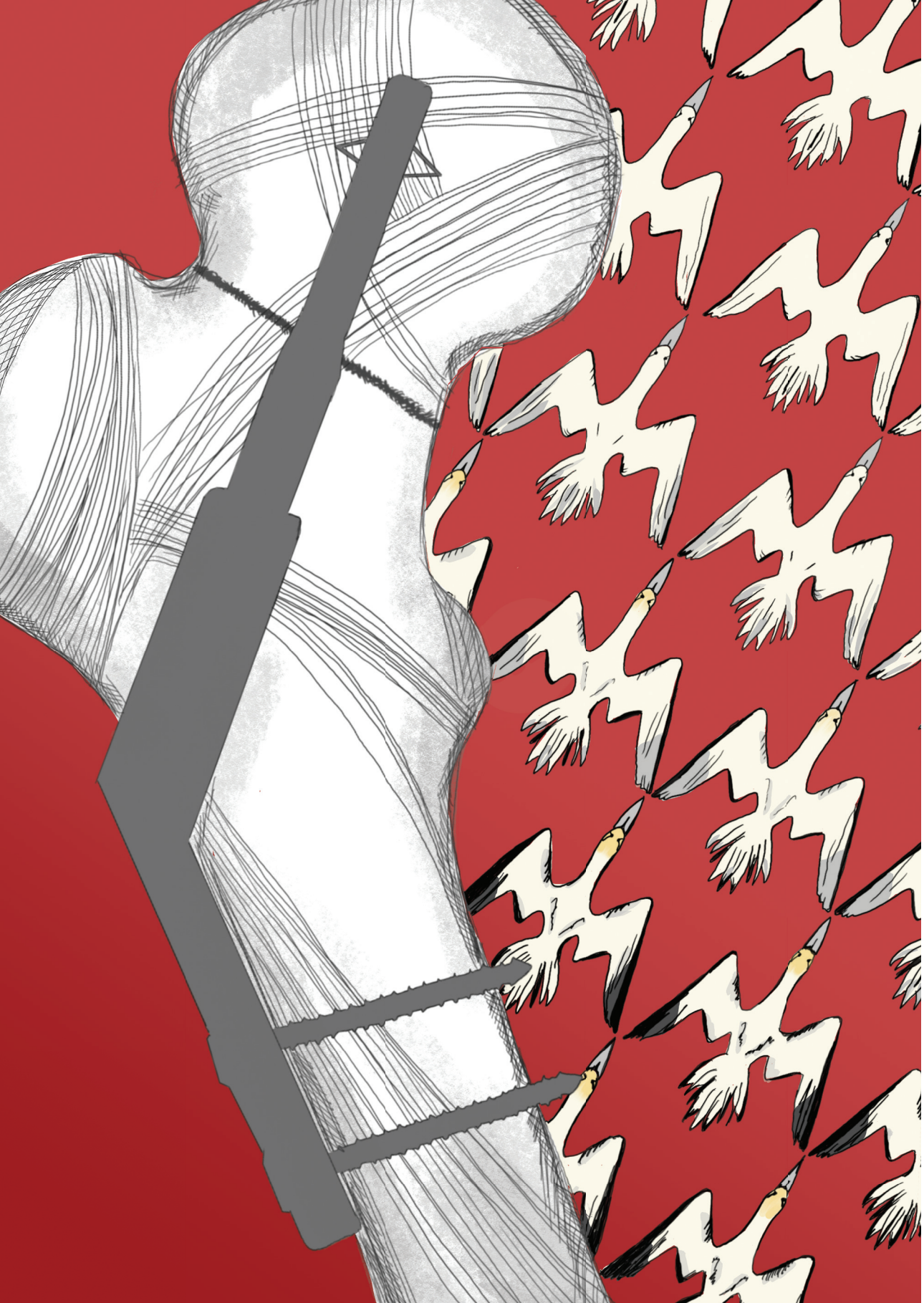
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# Chapter 2

What makes fixation of femoral neck fractures fail? A systematic review and meta-analysis of risk factors

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# ABSTRACT

## *Introduction*

This systematic review aims to provide an overview of predictors for failure of treatment of displaced femoral neck fracture (dFNF) with internal fixation and quantify their risk of fixation failure in a meta-analysis.

## *Patients and Methods*

PubMed, Embase, Web of Science, Cochrane Library, and EMCare were searched for original studies published from January 2000, including adult patients with an internally fixated dFNF, that reported data on predictors for fixation failure defined as revision surgery due to non-union, avascular femoral head necrosis or cut-out of implant. RevMan version 5 software was used to pool univariable Odds Ratio's (OR) for predictors of fixation failure by means of a random effects model.

## *Results*

This review included 16 articles (15 articles cohort studies and one randomised trial). Twenty-four predictors for fixation failure were identified and analysed, 16 of which were evaluated in just one study. Data of 7 predictors were pooled in a meta-analysis. Female sex (OR 1.78, 95% confidence interval [CI] 1.26–2.52), smoking (OR 3.64, 95% CI 1.68–7.91), age >50 years (OR 3.64, 95% CI 1.68–7.91), inadequate fracture reduction (OR 2.28, 95% CI 1.62–3.22), fixation with cannulated screws (CS) or pins compared to fixed angle devices (OR 2.16, 95% CI 1.03–4.54) were identified as significant predictors for fixation failure.

## *Conclusion*

This study can help surgeons to choose the preferred treatment for patients with a dFNF and substantiate future algorithms and guidelines for treatment of FNF.

## INTRODUCTION

Treatment of displaced femoral neck fractures (dFNF) remains challenging.<sup>1</sup> dFNF are treated with either reposition and internal fixation (IF) or (hemi)arthroplasty. Considering the pros and cons of these two treatment modalities, (hemi)arthroplasty is known to be associated with a higher infection rate than IF and can be complicated by hip dislocation.<sup>2</sup> Also peri-prosthetic fractures may occur with devastating consequences. Furthermore, most prostheses need revision surgery after around 25 years.<sup>3,4</sup> Alternatively, treatment with IF may lead to avascular necrosis (AVN) of the femoral head, resulting in non-union of the fracture or cut-out of the implant.<sup>5</sup> These complications result in more reoperations than treatment with a prosthesis.<sup>2,6,7</sup> Failure rates of dFNF treated with IF up to 48% have been reported.<sup>2</sup> Despite countless publications on FNF treatment, it is still unclear which patients with a dFNF have a high risk of unsuccessful treatment with IF and may be better off with a prosthesis. Today treatment algorithms for dFNF are mainly based on age<sup>8,9</sup> stating that younger patients are preferably treated with fracture reduction and IF, whereas older patients are preferably treated with (hemi)arthroplasty. There is no clear consensus from what age patients with a dFNF would better be treated with a prosthesis.<sup>8-10</sup> The treatment outcome with IF is influenced by many factors. Predictors for failure of treatment with IF are mentioned in literature.<sup>11-15</sup> Some predictors are patient-related (gender, osteoporosis, smoking, comorbidities), while others are fracture-related (displacement, posterior cortex comminution) or operation-related (reposition of the fracture, choice and position of the implant).

To our knowledge there is no overview in literature of all known potential predictors of failure of treatment of dFNF with IF. An overview of predictors and the substantiation of their role in treatment failure may help surgeons choose the preferred treatment strategy for patients with a dFNF. This systematic review of the literature aims to provide an overview of predictors for failure of treatment of dFNF with IF and quantify their risk of fixation failure in a meta-analysis.

## METHODS

This review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.<sup>16</sup> The review protocol was registered in the international prospective register of systematic reviews PROSPERO (protocol number CRD42020210914).

## Eligibility criteria

We selected all types of original studies, available in English, German or Dutch, published from January 2000, including patients of 18 years or older with a dFNF treated with any form of IF, that reported the odds ratios (ORs) of predictors of failure of treatment (defined as any revision surgery such as conversion to arthroplasty, girdle stone, core decompression, vascular fibular graft, valgus (intertrochanteric) osteotomy due to non-union, avascular femoral head necrosis or cut out of implant) or that provided sufficient information to calculate the ORs. No minimal duration of follow up was required.

## Exclusion criteria

Studies of which the full text was not available, were excluded. Reviews, surveys, current (management) concepts, editorials, commentaries, animal studies or cadaveric studies, meeting abstracts, conference proceedings, case studies and case series (N<20) were also excluded.

## Search strategy and selection process

A systematic search was conducted in PubMed, Embase, Web of Science, Cochrane Library, and EMCare on August 21, 2020, which was updated on November 11, 2021 and July 19, 2022. The search strategy was developed with help of an experienced medical librarian and adjusted for each specific database. The search terms included 'displaced femoral neck fractures', 'internal fixation', 'revision surgery/re-operation', 'predictors for failure' and their synonyms. The search strategy was validated by confirming that 4 predefined relevant articles were identified using the search terms.<sup>17-20</sup> Details of the search strategy are provided in Supplementary Material 1. After removal of duplicates, title and abstract of the identified records were independently screened by two reviewers (JHK and MFD) and documented in Rayyan Systems Inc<sup>21</sup>, using the predetermined eligibility criteria and exclusion criteria. Excluded articles were classified according to the reason of exclusion. Disagreements were discussed with a third author (WHR or IBS). Next, the full texts of the selected articles were assessed for eligibility using the same criteria. The reference lists of the included articles were searched by hand to identify relevant publications that were missed in the search.

## Data extraction and quality of evidence assessment

Data-extraction from the full-text articles was done by two independent reviewers (JHK and MFD) using a previously designed data extraction form. Any disagreements were discussed with a third author (PK). Information of the following study characteristics were extracted: first author's name, year of publication, study design, number of patients included for analysis, patients' mean age, exclusion criteria, type of implant used for fracture fixation, mean follow up, number and percentage of patients with and without the investigated potential predictors for failure, in the groups with and without fixation failure (reoperation).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to determine certainty in the pooled estimates of association between prognostic factors and future outcome for 5 domains including risk of bias, imprecision, inconsistency of results across studies, indirectness, and publication bias.<sup>22</sup> Risk of bias in the individual studies was assessed using the Quality in Prognostic Studies (QUIPS) tool (supplementary data 2).<sup>23</sup> Inconsistency of results across studies was assessed by analysing the Forest Plots and by the amount of statistical heterogeneity in results ( $I^2$ ) between the studies included in the meta-analysis. Imprecision of the estimates was based on whether the 95% confidence interval (CI) excluded an OR of 1 and the width of the CI. Indirectness evaluates whether the study population and outcome were comparable between studies. The probability of publication bias was visually assessed using funnel plots.

### Data synthesis

RevMan version 5 software<sup>24</sup> was used to pool univariable OR's for predictors of fixation failure by means of a random effects model. The  $I^2$  statistic, indicating the percentage of variation across studies due to statistical heterogeneity, was used to measure the inconsistency of the studies' outcomes, and was qualified as follows: 0% to 40% (might not be important); 30% to 60% (may represent moderate heterogeneity); 50% to 90% (may represent substantial heterogeneity); 75% to 100% (considerable heterogeneity).<sup>25</sup> Sensitivity analysis was done by leaving out individual studies from the analysis to assess their effect on the overall results.

## RESULTS

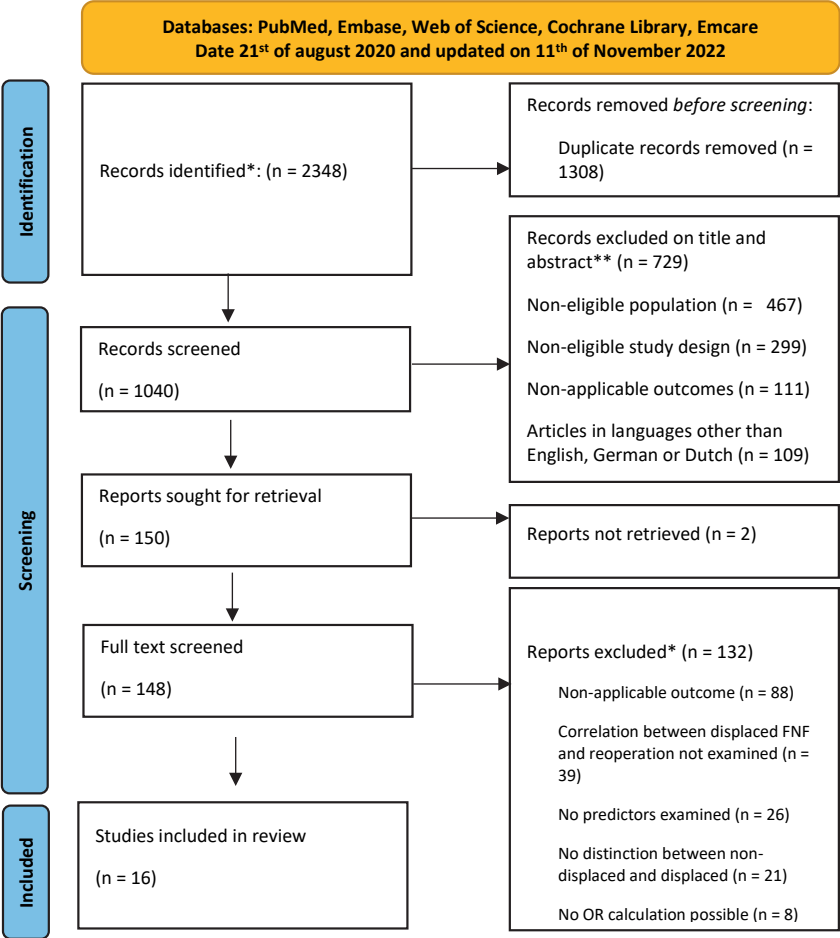
### Study identification and selection

The literature search, including the update, yielded a total of 2348 regular references (1040 unique records). The selection process with reasons for exclusion of studies is presented in Figure 1. A total of 16 articles were included for analysis.<sup>19,20,26-39</sup>

### Study characteristics

The characteristics of the included studies with the definitions of the investigated predictors are outlined in Table 1. All studies but one were prospective or retrospective cohort studies. One study comprised a randomised controlled trial. The studies were conducted in China (1), Denmark (1), Israel (2), the Netherlands (4), Scotland (1), Sweden (2), Taiwan (1), and the USA (4). Together, the 16 studies included a total of 2409 patients. Of these, 1874 patients (1875 dFNFs) met the review's inclusion criteria and were eligible for analysis. Although the inclusion criteria for the patients in the studies were similar, there was a wide range of exclusion criteria. In total 31 different exclusion criteria were used, 18 of which were only mentioned in one study (Table 1). The mean age of the patients in the included studies

ranged from 38–84 years old. In four of the 16 studies the patients’ mean age was above 60 (n=778). All studies had a mean follow up of at least 12 months (range 12–150 months). The overall reoperation rate was 24.3% (455 of 1875 dFNFs), ranging from 6.7–40.5%.



**Figure 1.** PRISMA 2020 flow diagram for systematic reviews. FNF, Femoral neck fracture. OR, Odds ratio. \*Details of the search strategy are reported in Supplementary Material 1.

\* Some studies were excluded due to multiple reasons.

### Risk of bias and quality of evidence assessment

The risk of bias within the studies was moderate to high (supplementary material 2). Risk of bias due to confounding was assessed highest, because only a few potentially important confounders were accounted for in the analysis in the individual studies. Yet as stated in our introduction there is a wide range of factors that potentially influence the reoperation rate.

Table 1. Study characteristics and predictors for reoperation

Study details	Study design	Patients (n) included	Mean age (years)	Exclusion criteria	Treatment	Mean follow up (months)	Reoperations	Predictors investigated + cut off values	Significance predictors (p<0.05)
<b>Campenfeldt 2018</b>	Prospective cohort	120	58 (range 20-69)	Unable to walk Not living independently Psychotic disease Severe cognitive impairment Chronic renal failure Hyperparathyroidism Simultaneous fracture of the lower extremity Fracture older than 48 h Patients with previous pathology in the fractured hip	CRIF Two CS (Oimed)	24	28% (33/120)	Age (50-69 / 20-49 years) Gender (female/male) ASA score (3-4/1-2) <sup>a1</sup> Alcohol (AUDIT high/low) <sup>a2</sup> Smoking (yes/no) Mechanism of injury (high / low energy) Fracture reduction (fair-poor / good) <sup>a3</sup> Position of screws (not good / good) <sup>a4</sup> BMD femoral neck (low/normal) <sup>a5</sup>	Not significant (univariate model) Not significant (univariate model) Not significant (univariate model) Significant (multivariate model) Not significant (univariate model) Not significant (univariate model) Not significant (univariate model) Not significant (univariate model) Not significant (univariate model) Significant (multivariate model)
<b>Gardner 2014</b>	Retrospective cohort	69	43 (SD 13)	< 6 months follow up Pathologic fracture Fracture involving either trochanter or extending beyond the intertrochanteric line Femoral head fracture Acetabulum fracture	CRIF and ORIF CS with 6.5 mm or 7.3 mm cannulated partially threaded CS (Synthes, West Chester, PA) or SHS (Synthes, West Chester, PA).	18	28% (19/69)	Implants (CS/SHS) Smoking (yes/no) Fracture reduction (excellent / good-fair) <sup>b1</sup> Diabetes (yes/no) <sup>nd</sup> Alcohol abuse (yes/no) <sup>nd</sup> End stage renal disease (yes/no) <sup>nd</sup> Steroids (yes/no) <sup>nd</sup> Weight bearing status (as tolerated/protected) <sup>nd</sup> Gender (female/male)	Not significant (multivariate model) Not significant (multivariate model) Significant (multivariate model) Not significant (univariate model) Not significant (univariate model) Not significant (univariate model) Not significant (univariate model) Not significant (univariate model) Not significant (univariate model) Not significant (univariate model)

**Table 1. Continued**

Study details	Study design	Patients (n) included	Mean age (years)	Exclusion criteria	Treatment	Mean follow up (months)	Reoperations	Predictors investigated + cut off values	Significance predictors (p<0.05)
<b>Heetveld 2006</b>	Retrospective analysis of a prospective cohort	102	77	FNF > 48 hours old Advanced arthrosis of the ipsilateral hip Established rheumatoid arthritis Pathologic fracture	CRIF/ORIF DHS, DHS with anti rotational screw, 3 CS	24	38% (39/102)	Fracture reduction (inadequate/adequate) <sup>2c</sup> Implant positioning (inadequate/adequate) <sup>2b</sup> Overall operation technique (inadequate/adequate) <sup>2d</sup>	Significant (multivariate model) Not significant (multivariate model) Not significant (multivariate model)
<b>Heetveld 2005</b>	Prospective cohort	111	77	FNF > 48 hours old Advanced arthrosis of the ipsilateral hip Established rheumatoid arthritis Pathologic fracture	DHS, DHS with anti rotational screw, CS	24	41% (45/111)	Osteoporosis measured using the femoral neck (osteoporosis/osteopenia+normal) <sup>2d</sup>	Not significant (univariate model)
<b>Hoshino 2016</b>	Retrospective cohort	62	39 (SD 12)	Treated with parallel screw configurations, proximal femoral locking plates or cephalomedullary nails < 6 months follow-up	ORIF and CRIF (<5%) The dynamic hip screw (DHS) and the dynamic helical hip system (DHHS) (DePuy Synthes, Inc., West Chester, PA) Pauwel screw, either a solid 4.5-mm or cannulated 7.3-mm lag screw	17	30% (19/63)	Implants (pauwel screws/ fixed angle device)	Significant (univariate model)

Table 1. Continued

Study details	Study design	Patients (n) included	Mean age (years)	Exclusion criteria	Treatment	Mean follow up (months)	Reoperations	Predictors investigated + cut off values	Significance predictors (p<0.05)
<b>Huang 2010</b>	Retrospective cohort	104	47	Inadequate reduction Bilateral hip fracture Open fracture Previous fracture Symptomatic osteoarthritis of the hip before injury Rheumatoid arthritis Pathologic fracture and a malignant disease No complete sets of preoperative, postoperative and follow-up radiographs	CRIF Percutaneous fixation with parallel CS(7.0 mm in diameter, Synthes)	57	30% (31/104)	Posterior wall disruption (yes/no) <sup>e1</sup>	Significant (univariate model)
<b>Kalland 2019</b>	Prospective RCT	114	ND for dFNF	Fracture of the contralateral hip	Pinloc or 2 Hansson Pin System	12	22% (25/114)	Implants (Hansson Pins/ Pinloc) Age (≥70/50-69)	Not significant (univariate model) Not significant (univariate model)
<b>Kalsbeek 2018</b>	Prospective cohort	106	52 (range 23-60)	Any implant other than DLBP Pathological fracture Concomitant fractures of the lower limb Symptomatic arthritis Local infection or inflammation Inadequate local tissue coverage Any mental or neuromuscular disorder, which would create an unacceptable risk of fixation failure, complications or evaluation postoperatively.	Dynamic locking blade plate	12	13% (14/106)	Gender (female/male) Tip Apex Distance (>25mm/≤25mm) <sup>f1</sup> Reposition (malreduction/ good reduction) <sup>f2</sup>	Not significant (univariate model) Not significant (univariate model) Not significant (univariate model)
<b>Kenan 2015</b>	Retrospective cohort	27	44 (range 23-59)	none	CRIF/ORIF Three 7.3 mm CS	150 (range 96-204)	14.8% (4/27)	Age (50-60/<50)	Significant (univariate model)

**Table 1. Continued**

Study details	Study design	Patients (n) included	Mean age (years)	Exclusion criteria	Treatment	Mean follow up (months)	Reoperations	Predictors investigated + cut off values	Significance predictors (p<0.05)
<b>Marchand 2022</b>	Retrospective cohort	77	38 (range 18-59)	Severe osteoarthritis Bone metabolism disorders Fractures associated with a fracture to the ipsilateral acetabulum	DHS or DHHS	12	19.5%(15/77)	Implants (DHS/DHHS)	Not significant (univariate model)
<b>Nyholm 2020</b>	Retrospective cohort	537 (deceased patients excluded)	69 (range 21-102)	Foreign citizens Incorrect date of surgery in DFDB Alternative surgical technique Dead prior to postoperative radiography New fracture of the hip before postoperative radiography Screws, Stryker; or 8.0-mm Asnis 6.5-mm Hansson Pins, Swemac Orthopaedics	8.0-mm Olmed screws and 6.5 or 7.3-mm Canulated screws, DePuy-Synthes, Johnson & Johnson MD&D; 8.0-mm Asnis Screws, Stryker; or 6.5-mm Hansson Pins, Swemac Orthopaedics	12	23% (124/537)	Age (≤60/>60) Gender (female/male) Time to surgery (<24h/>24h) Severe displacement (mildly/severely displaced) <sup>§1</sup> Insufficient reduction (partly-not/fully reduced) <sup>§2</sup> Protrusion of an implant (yes/no) <sup>§3</sup> Bone quality (CTI) (≤0.5/>0.5) <sup>§4</sup> Angulation of implants (≤125°/>125°) <sup>§5</sup>	Not significant (multivariate model) Significant (multivariate model) Significant (multivariate model) Significant (multivariate model) Significant (multivariate model) Significant (multivariate model) Not significant (multivariate model) Not significant (multivariate model)
<b>Patterson 2020</b>	Retrospective cohort	234	45 (18-65)	Pathologic FNF Ipsilateral acetabular, femoral head, shaft, or supracondylar femur fracture Less than minimum 6-month follow-up	CRIF, ORIF with sliding hip screw or cephalomedullary nail or CS	18 (range 6-130)	26% (55/212)	Reduction technique (ORIF/CRIF)	Significant (univariate model)
<b>Stearns 2009</b>	Retrospective cohort	78	56 (range 18-65)	Incomplete records	SHS and CS	43	6,7% (4/59)	Alcohol abuse (alcohol abuse/no abuse) <sup>§1</sup>	Not significant (univariate model)

**Table 1. Continued**

Study details	Study design	Patients (n) included	Mean age (years)	Exclusion criteria	Treatment	Mean follow up (months)	Reoperations	Predictors investigated + cut off values	Significance predictors (p<0.05)
<b>Thein 2014</b>	Retrospective cohort	78	54 (SD 16)	Pathological fractures Previous surgery on the ipsilateral hip or femur Failure to complete 1 year of follow-up.	CRIF Targon FN or multiple CS.	28.7	25,6% (20/78)	Implant (CS/Targon FN)	Significant (univariate model)
<b>van Dortmont 2000</b>	Randomized controlled trial	28	84 (range 72-92)	ND	CRIF Three cannulated AO/ASIF screws.	14 (range 0.5-60)	1,4% (4/28)	Reduction (Inadequate/adequate) <sup>a1</sup>	Not significant (univariate model)
<b>Xiong 2019</b>	Retrospective cohort	46	50 (range 19-60)	Pathological fracture Malignant disease Open fracture Previous fracture Symptomatic osteoarthritis of the hip before injury Rheumatoid arthritis No complete sets of preoperative, postoperative, and follow-up radiographs	Closed reduction and fixation with multiple cannulated screws (6.5mm in diameter) in inverted triangle or diamond configuration	22 (range 12-36)	9% (4/46)	Inferior calcar buttress reduction pattern <sup>a1</sup> (non-anatomical/anatomical)	Not significant (univariate model)

AP: anterior posterior; AVN: avascular necrosis; CRIF: closed reduction and internal fixation; CS: Cannulated screws; DFDB: Danish Fracture Database; dFNF: displaced femoral neck fracture; DHHS: dynamic helical hip system; FNF: femoral neck fracture; IF: internal fixation; ISS: injury severity score; MD: not described; ORIF: open reduction and internal fixation; OTA: Orthopaedic Trauma Association; SFNF: stress fracture of the femoral neck; SHS: sliding hip screw.

a1: American Society of Anesthesiologists classification (ASA score).

a2: Alcohol Use disorder Identification Test (AUDIT) A total score of 8 or more in men or 5 in women indicates a strong likelihood of hazardous or harmful high alcohol consumption.

a3: Good reduction was a displacement of < 2 mm, a posterior angulation of <10 between the femoral head/neck compared to the femoral shaft on a lateral radiograph and a Garden angle of 160° to 175°.

a4: The screw position was considered as optimal when the distal screw was positioned on the femoral calcar and introduced at the level of the lesser trochanter. The tip of both screws should be less than 5 mm from the subchondral bone and the proximal screw should be parallel positioned (< 10°) and at least 2 cm apart from the distal screw. On the lateral projection the screws should lie on the central or posterior third of the femoral head and neck and be parallel. The position was considered as suboptimal if one or more of these criteria were not fulfilled.

a5: BMD: Bone Mass Density; T-scores of femoral neck were calculated for patients between 50-69 years and Z-scores in patients 20-49 years of age according to the International Society of Clinical Densitometry. A T-score > -1 SD (standard deviation) was considered a normal BMD, osteopenia if T-score of -1 to -2,49 SD and osteoporosis if T-score < -2.5 SD. In patients (20-49 years), a Z-score < -2 SD was considered as a low BMD. Low BMD was defined as osteopenia/osteoporosis in patients between 50-69 years or Z-score < -2 SD in patients 20-49 years old. b1: Excellent (<2 mm displacement and/or <5 degrees of angulation), good (2-5mm displacement and/or 5-10 degrees of angulation), fair (5-10 mm displacement and/or 10-20 degrees of angulation) or poor (>10 mm displacement and/or >20 degrees of angulation).

- c1: PSS: Physiologic Status Score; high PSS is defined as mobile with no or one walking aid outside the home, living independently at home or partial dependence on social services/relatives, good cognitive function and ASA 1-2.
- c2: Adequate reduction: on anteroposterior view within 160 to 180 degrees (Garden index). In the lateral view 10 degrees of anteversion or retroversion is acceptable.
- c3: Implant positioning: CS had to be inserted according to the following criteria: (1) two screw positions within 3 mm of the inferior and posterior cortices of the femoral neck calcar, (2) parallelism of the inserted screws to within 10°, (3) screw tips to within 5 mm of the subchondral bone in the femoral head, (4) minimal screw diameter of 6.5 mm, and (5) screws should be inserted in a manner to lag and not across the fracture site. A SHS had to be inserted according to the following criteria: (1) screw tip on anteroposterior and lateral views of the hip are less than 25 mm from the apex of the femoral head (tip apex distance) and not anterior or superior in the femoral head, (2) screw in the central or dorsal part of the femoral head and not crossing the fracture line on the lateral view, and (3) two- (preferable) or four-hole side-plates were acceptable.
- c4: Adequate reduction and implant positioning combined.
- d1: Osteoporosis is a T score of below -2.5 SD (standard deviation).
- e1: The posterior wall of the femoral neck was considered to be disrupted if a fragment was observed on the antero-posterior or lateral plain radiograph of the affected hip or on an antero-posterior radiograph of the pelvis.
- f1: Tip-apex distance: 25mm is the cut off value.
- f2: The Garden Alignment Index was used. The acceptable range of reduction is a 160 to 180° angle.
- g1: Mildly displaced=Garden II with > 20° posterior tilt or Garden III type fracture. Severely displaced=Garden type IV FNF.
- g2: Fully reduced = Non-displaced in anteroposterior (AP) view, < 10° posterior tilt (PT). Partly/not reduced = Non-displaced in AP view, ≥ 10° PT or displaced in AP view.
- g3: Implant protrusion into the joint (evaluated by eye).
- g4: Cortical thickness index (CTI) measured as the part of the diameter of the femoral shaft that consisted of cortex measured 10 cm below the tip of the trochanter minor.
- g5: Angle of implants to the lateral cortex of the femoral shaft in anteroposterior view.
- h1: Alcohol abuse = self-admitted chronic alcohol abuse (> 40 units per week) or documented evidence of complications of long-term abuse (such as Korsakoff's Syndrome or alcoholic liver disease).
- i1: Adequate fixation is a Gardens angle within 170-179°, a lateral Gardens angle not exceeding 20° and a Western Infirmary Glasgow angle within 140-149°.
- j1: Anatomic cortical apposition with smooth inferior cortex apposition vs positive cortical apposition obtained calcar support. The proximal head-neck fragment is slightly superiorly displaced intentionally (less than one cortex thickness or 4 mm) to the distal fragment, so that the inferior cortex of the proximal head-neck fragment can be buttressed by the calcar cortex of the distal neck fragment.

**Table 2.** Quality of evidence using the GRADE approach\*

Predictor	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Certainty of estimates
Gender	Moderate	High	Moderate	High	High	High
Smoking	Moderate	High	Moderate	High	High	High
Alcohol abuse	Moderate	Low	Low	High	High	Moderate
Fracture reduction	Moderate	High	High	High	High	High
Bone quality	Low	Low	Low	Moderate	High	Moderate
Cannulated screws vs Fixed angle devices	Moderate	Low	Moderate	High	High	Moderate
Age (>50y, <50y)	Moderate	Moderate	High	High	High	High
Screw/implant position	Low	Very low	Moderate	High	High	Moderate
Posterior wall disruption	Very low	NA	Low	High	NA	Low
ASA classification	Very low	NA	Very low	High	NA	Very low
Mechanism of injury	Very low	NA	Very low	High	NA	Very low
Diabetes	Very low	NA	Very low	High	NA	Very low
End stage renal disease	Very low	NA	Very low	High	NA	Very low
Steroid use	Very low	NA	Very low	High	NA	Very low
Weight bearing status	Very low	NA	Very low	High	NA	Very low
Overall operation technique	Very low	NA	Low	Moderate	NA	Low
Tip Apex Distance	Very low	NA	Very low	High	NA	Very low
DHS vs DHHS	Very low	NA	Very low	High	NA	Very low
Time to surgery	Low	NA	Low	High	NA	Low
Displacement	Low	NA	Moderate	High	NA	Low
Protrusion of an implant	Low	NA	Low	High	NA	Low
Angulation of implant	Low	NA	Low	High	NA	Low
Closed or open reduction	Very low	NA	Low	High	NA	Low
Non-anatomic cortical buttress reduction technique	Very low	NA	Very low	High	NA	Very low

\***Certainty in the estimates was graded as previously described by Foroutan et al.<sup>22</sup>:**

**High:** We are very confident that the variation in risk associated with the prognostic factor (probability of future events in those with/without the prognostic factor) lies close to that of the estimate.

**Moderate:** We are moderately confident that the variation in risk associated with the prognostic factor (probability of future events in those with/without the prognostic factor) is likely to be close to the estimate, but there is a possibility that it is substantially different.

**Low:** Our certainty in the estimate is limited: the variation in risk associated with the prognostic factor (probability of future events in those with/without the prognostic factor) may be substantially different from the estimate.

**Very low:** We have very little certainty in the estimate: the variation in risk associated with the prognostic factor (probability of future events in those with/without the prognostic factor) is likely to be substantially different from the estimate.

NA: Not assessed because evaluated in just one study.

Also in some studies the potential predictors were poorly defined. No publication bias was found by the visual distribution of funnel plots (supplementary material 3).

Overall, the quality of evidence for the prognostic factors included in the meta-analysis were assessed as moderate to high (Table 2). The prognostic factors that were evaluated in one study were rated low to very low. For predictors evaluated by only one study inconsistency and publication bias could not be assessed. We are certain of the study population and outcome were comparable between studies due to our strict eligibility criteria so indirectness was rated high for almost all predictors.

### **Predictors for reoperation after fixation of dFNF**

Twenty-four predictors for treatment failure (reoperation) were identified and analysed, 16 of which were evaluated in just one study (supplementary material 4). Definitions of the predictors in the individual studies are shown in Table 1. We were able to pool the data of 7 predictors in a meta-analysis. Regarding the patient characteristics, higher risk of reoperation was found for female patients compared to male patients (OR 1.78, 95% CI 1.26–2.52; Figure 2), for age >50 years compared to age ≤50 years (OR 3.64, 95% CI 1.68–7.91; Figure 3), and for smoking compared to no smoking (OR 2.27, 95% CI 1.12–4.62; Figure 4). Alcohol abuse (Figure 5) and bone quality (Figure 6) were not found to be statistically significant risk factors for re-operation. Regarding treatment-related factors, higher risk of reoperation was found for inadequate fracture reduction (OR 2.28, 95% CI 1.62–3.22; Figure 7), and for cannulated screws (CS) or pins compared to fixed angle devices (OR 2.16, 95% CI 1.03–4.54; Figure 8).

For the predictors bone quality and type of implant there was moderate statistical heterogeneity, respectively 32 and 46%. For bone quality, the heterogeneity seemed mainly due to the definition of good and lesser bone quality, which differed in all three studies (Table 1).<sup>20,26,32</sup> Therefore no sensitivity analysis was performed. Considering the predictor ‘type of implant’, heterogeneity may have been caused by the fact that all studies used slightly different CS and fixed angle devices.<sup>28,30,34,37</sup> Only Kalland used cannulated pins instead of CS as intervention technique.<sup>30</sup> If Kalland was left out of the analysis, the statistical heterogeneity decreased from 46 to 37% and the OR of CS versus fixed angle devices increased to 2.84 (95% CI 1.21–6.66).

Fifteen predictors were investigated in only one study and one predictor (adequate position of the implant) was evaluated in two studies that could not be combined due to heterogeneity of the implant material. Four of these sixteen predictors were statistically significant in the individual studies: presence of posterior wall disruption (OR 4.50; 95% CI 1.84–10.98)<sup>29</sup>, adequate overall operation technique (OR 4.17; 95% CI 1.61–10.81)<sup>27</sup>, displacement of the femoral head (OR 2.77; 95% CI 1.83–4.22)<sup>32</sup>, angulation of the CS to the lateral cortex (OR

2.37; 95% CI 1.04–5.42)<sup>32</sup> (supplementary material 4). In the study by Camperfeldt et al. no association with reoperation was found for ASA classification and mechanism of trauma.<sup>26</sup> In the study by Gardner reoperation was not associated with diabetes, end-stage renal disease, steroid use and weight-bearing status.<sup>37</sup> In the study by Nyholm no association with reoperation was found for time to surgery and protrusion of the implant.<sup>32</sup> Reoperation was also not related to the tip-apex distance<sup>20</sup>, closed reduction<sup>38</sup>, and non-anatomic cortical buttress reduction<sup>36</sup>. Marchand et al. did not find any difference in reoperation between two fixed angle devices (the dynamic hip screw (DHS) and the dynamic helical hip system (DHHS)).<sup>39</sup> Adequate position of the implant was no statistically significant predictor in the studies by Camperfeldt and Heetveld.<sup>26,27</sup>

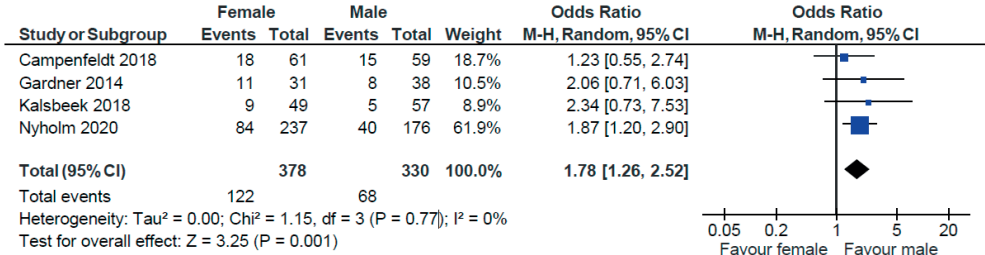


Figure 2. Forest plot of the comparison of female versus male.

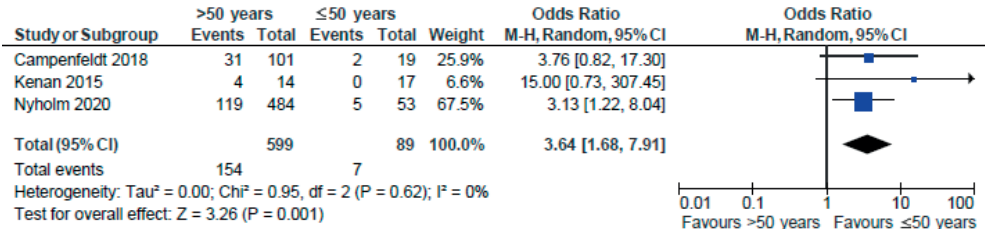


Figure 3. Forest plot of the comparison of age >50 years old versus ≤50 years old.

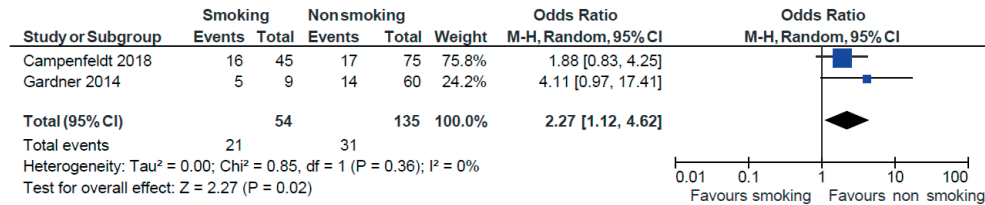


Figure 4. Forest plot of the comparison of smoking versus non-smoking.

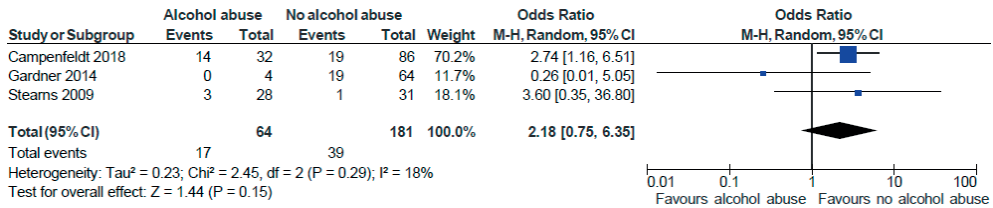


Figure 5. Forest plot of the comparison of alcohol abuse versus no alcohol abuse.

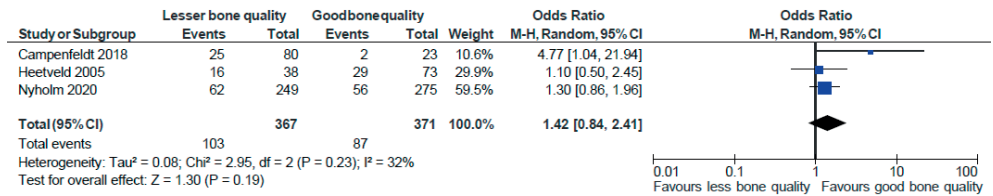


Figure 6. Forest plot of the comparison of good bone quality versus lesser bone quality.

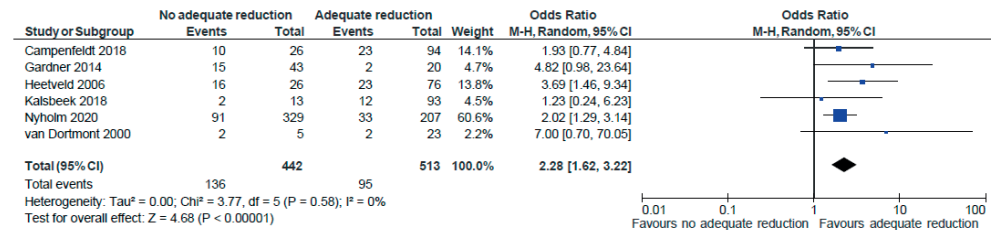


Figure 7. Forest plot of the comparison of adequate reduction versus no adequate reduction of the femoral neck fracture.

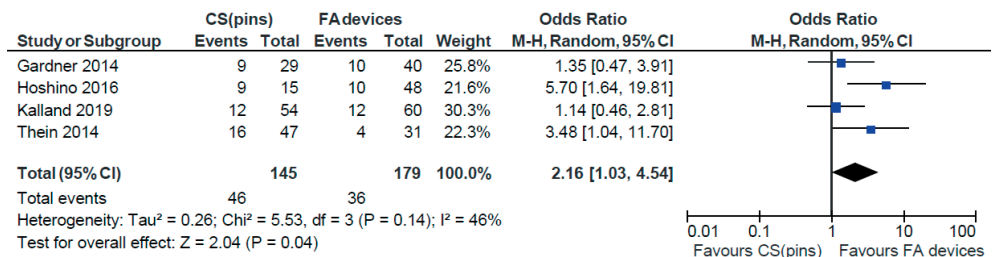


Figure 8. Forest plot of the comparison of cannulated screws (CS) or pins versus a fixed angle

## DISCUSSION

In this systematic review and meta-analysis we identified predictors for failure of treatment with IF for dFNF. The results of the meta-analysis show five risk factors for reoperation: female gender, age >50 years, smoking, inadequate fracture reduction, fixation with cannulated screws or pins. Another four predictors were identified in single studies: presence of posterior wall disruption, adequate overall operation technique, displacement of the femoral head, and angulation of the CS to the lateral cortex.

Four articles were included in our meta-analysis that investigated the effect of gender on treatment failure (Figure 2).<sup>19,26,32,37</sup> We found that female patients appear to have a higher risk to be reoperated than men (OR 1.78, 95% CI 1.26–2.52). This might be explained because the femoral neck shaft angle is lower in women compared to men.<sup>40</sup> This results in a larger moment arm which leads to more downward force on the collum femoris. In theory, this could lead to an earlier cut-out. Yet, other authors deny the existence of this anatomic difference between men and women.<sup>41</sup> Another explanation could be that bone quality in postmenopausal women is inferior compared to men.<sup>42</sup> However, the three studies in our meta-analysis for bone quality did not show an effect of bone quality on the failure rate (Figure 6).<sup>20,26,32</sup> Age was also identified as a predictor for reoperation (OR 3.64, 95% CI 1.68–7.91). In this meta-analysis we used 50 years of age as a cut-off point because then we could combine the results of three studies. With increasing age bone quality declines and the incidence of other comorbidities rises.<sup>42</sup> In literature the cut-off point for age for fixing dFNF with IF usually lies between 60–70 years old.<sup>8,9</sup> We believe there is not an exact age above which arthroplasty can be advised as age is just one of many factors that affect the reoperation rate of patients with dFNF treated with IF.

Two studies investigated smoking as a predictor for reoperation.<sup>26,37</sup> Although the association was not statistically significant in these individual studies, smoking became a statistically significant predictor of treatment failure after we combined the data of these studies. Smoking causes peripheral artery disease.<sup>43</sup> Thus, smoking may compromise the vascularisation of the femoral neck and head, which we believe to be one of the most important factors for union and viability of the femoral head. Also smoking is associated with slower healing and non-union of fractures.<sup>44</sup>

Fracture reduction was one of the most investigated predictors in this review.<sup>19,26,27,32,35,37</sup> All studies accepted fracture reduction with a maximum malalignment of around 10–20 degrees in the anteriorposterior plane and 10 degrees in the lateral plane. Combining the results of these studies in our meta-analysis showed a statistically significant association between an inadequate reduction and reoperation. An adequate reduction in combination

with stable fixation will provide the most optimal conditions for (re)vascularisation of the femoral head.

It could be that CS provide less stability after adequate reduction. Earlier biomechanical and cadaver studies support the finding that fixed-angle devices are superior to CS in stabilizing FNF.<sup>45,46</sup> The results of four studies comparing CS or pins with a fixed-angle device are in line with those findings.<sup>28,30,34,37</sup> The meta-analysis of these four studies showed a favourable outcome for the fixed angle devices, which may provide better stability.

Besides type of implant the adequate placement of the implant is also important. Two studies investigated placement of implants<sup>26,27</sup>, but were not combined in a meta-analysis due to differences in study design. Both studies investigated the placement of CS, yet Campenfeldt investigated fixation with 2 CS and Heetveld with 3 CS. Also, both studies used different definitions of adequate screw placement (Table 1). Furthermore, Heetveld also looked at the placement of the sliding hip screw and its relation to reoperation. The data of CS and the sliding hip screw in this study was combined. Despite these differences, implant positioning in both studies did not affect the reoperation rate. Another recently published study also showed that the position of a sliding hip screw in the femur does not influence the revision rate.<sup>47</sup> The position of three cannulated screws on the other hand does affect the revision rate of FNF according to Schottel et al.<sup>47</sup>

We found a significant association between initial angle of the CS to the lateral cortex using the data of Nyholm.<sup>32</sup> Although Nyholm et al. also found a similar result in their univariable Cox regression analysis, the association was no longer statistically significant in their multivariable analysis. We could not find any literature that substantiates the supposed association between the angulation of CS to the lateral cortex.

One study stated that the overall operation technique is also of significant influence on the outcome of treatment of dFNF and should therefore not be delegated to inexperienced surgeons.<sup>27</sup> The results in that study are difficult reproduce due to a complex and extensive definition of a good overall operation technique (Table 1). Although these results are difficult to compare with other literature, the importance of adequate reduction and placement of the implant essential for proper stability and therefore a successful treatment.<sup>48-50</sup>

Presence of posterior wall disruption was identified as a predictor of revision surgery in a study by Huang et al.<sup>29</sup> Due to posterior comminution, a disrupted posterior cortex will remain after reduction, which could lead to more instability.<sup>51,52</sup> Some authors even advocate the use of a fibular graft to buttress the posterior cortex.<sup>53</sup>

Nyholm stated that severe displacement of the femoral head (Garden type IV) is also associated with a higher reoperation rate.<sup>32</sup> In another, slightly older study, the 4-grade Garden system did not predict an unfavorable outcome (defined as change of position of the screws, collapse of the fracture by more than 20 mm, perforation of the femoral head by screw(s), or salvage with arthroplasty).<sup>54</sup> We could not find other studies that compared the reoperation rate of Garden type III and IV FNF.

## Conclusion

In conclusion, our systematic review and meta-analysis identified female gender, age above 50 years old, smoking, inadequate fracture reduction and treatment with cannulated screws as predictors for reoperation of patients with dFNF treated with IF. Female patients with a dFNF above 50 years of age that smoke have a high risk of failure of treatment. Furthermore if a dFNF cannot be properly repositioned the surgeon might consider to convert to an arthroplasty at a low threshold and if the dFNF is adequately repositioned it should preferably be fixated with a fixed angle device. This study can help surgeons to choose the preferred treatment for patients with a dFNF and substantiate future treatment algorithms and guidelines for treatment of FNF.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.injury.2022.11.042 .

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