

# The epidemiology and risk factors for recurrence after inguinal hernia surgery

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## ARTICLES INCLUDED IN THE THESIS

1. Burcharth J, Pedersen M, Bisgaard T, Pedersen C, Rosenberg J. Nationwide Prevalence of Groin Hernia Repair. *PLoS One* 2013;8:e54367 (1).
2. Burcharth J, Andresen K, Pommergaard H-C, Bisgaard T, Rosenberg J. Recurrence patterns of direct and indirect inguinal hernias in a nationwide population. *Surgery* 2013, Oct 25 (Epub ahead of print) (2).
3. Burcharth J, Andresen K, Pommergaard H-C, Bisgaard T, Rosenberg J. Direct inguinal hernias and anterior surgical approach are risk factors for female inguinal hernia recurrences. *Langenbecks Arch Surg* 2014;399:71-6 (3).
4. Burcharth J, Pommergaard H-C, Bisgaard T, Rosenberg J. Patient related risk factors for recurrence after inguinal hernia surgery – a systematic review and meta-analysis of observational studies. Submitted (4).

## INTRODUCTION

Operation for groin hernia is one of the most commonly performed general surgical procedures in both children and adults (5–7). A groin hernia is defined as a protrusion of a portion of an organ or abdominal content through and abdominal opening in the groin area, with a hernia sac covering the abdominal content. Groin hernias are classified according to anatomy (8) in inguinal hernias and femoral hernias, where inguinal hernias further are subdivided into indirect inguinal hernias (also known as lateral hernias) and direct inguinal hernias (also known as medial hernias) according to the anatomical relation to the inferior epigastric vessels (i.e. laterally or medially of the vessels) (9).

The reasons why inguinal hernias develop are largely unknown, and limited epidemiologic data exist regarding the detailed occurrence of inguinal and femoral hernias. It has been documented that the vast majority of groin hernias are inguinal hernias and only a smaller fraction being femoral hernias in both adults and children (1,7,10). Furthermore, it is known that the different subtypes of groin hernias occur at different rates according to age, since children almost exclusively develop indirect inguinal hernias (7), whereas a mixture of indirect inguinal hernias, direct inguinal hernias and femoral hernias occur in adults (10).

One of the largest challenges regarding groin hernia surgery is recurrence and this still remains a clinical problem, even though treatment modalities and technical aspects have improved. It has been reported that up to 13 % of all groin hernia procedures are being performed for recurrent hernias (11). The definitive reason for recurrence after inguinal hernia surgery still remains unclear and it has not been possible to identify single parameters or risk factors as being responsible. The identified risk factors for recurrence range widely and include controllable technical risk factors such as surgical technical methods (12,13), methods of anesthesia (14), mesh-fixation techniques (15), surgeon experience as well as hospital volume (16–18). Furthermore, a wide range of non-controllable patient-related risk factors such as gender (19,20), hernia anatomy (21), hernia type (22), mode of admission (23), family disposition (24), connective tissue composition (25), connective tissue degradation (26), smoking (27), and postoperative convalescence (28) all have been found to impact the risk of recurrence after inguinal hernia surgery in varying degrees. It is possible that the underlying pathophysiology of the different inguinal hernia types could affect the overall recurrence risk as well as the risk of developing a specific type of recurrent inguinal hernia.

An estimated 25% of all American males are expected to have an inguinal hernia at some point in their lifetime (29). Even though groin hernia surgery in the majority of cases does not cause any complications, it is not without risk being operated on. The most often occurring complications and unfortunate implications of groin hernia surgery besides recurrences, includes bleeding, post-operative infections, seromas, chronic pain, pain related sexual dysfunction and dysejaculation (30–32). Operation for recurrent hernias has a higher documented risk of carrying complications compared with primary hernia surgery (33). Simply because of the sheer number of groin hernia operations performed worldwide yearly, groin hernias constitute a significant socioeconomic problem (6,34), and every possible aspect that potentially could lower the recurrence rate should induce academic and clinical interest.

### **Hypothesis and objectives of Ph.D. thesis**

The main hypothesis for the studies included in this Ph.D. thesis was that the different types and subtypes of groin hernias have different pathophysiological properties, which could be shown by different age and gender epidemiology, different risk of recurrence and different patterns of recurrence. This has not yet been reported sufficiently in the literature and could have clinical consequences in terms of individualized risk assessed surgery and postoperative follow-up. Especially the relation between the type of hernia at the primary and recurrent procedure could provide a new view on hernia disease etiology. The objectives of this Ph.D were:

- To detailed describe the occurrence of inguinal and femoral hernia on a large-scale nationwide basis
- To detailed describe the occurrence of inguinal and femoral hernia on a large-scale nationwide basis
- To correlate the type of recurrences based on the primary hernia
- To provide an overview of the non-technical patient-related risk factors for recurrence after inguinal hernia recurrences

### **BACKGROUND**

#### ***The anatomic and evolutionary aspects of groin hernias***

By anatomy an indirect inguinal hernia protrudes through the internal inguinal ring within the cremaster fascia and extends down the spermatic chord. The hernia sac may be contained within the inguinal canal or it may exit from the external ring to descend towards the level of the testicles. A direct inguinal hernia protrudes through the posterior wall of the inguinal canal medially to the inferior epigastric vessels by destroying or stretching the relatively thin and unresponsive fascia transversalis. A femoral hernia protrudes through the fascia transversalis medially of the femoral vein into the femoral canal under the inguinal ligament (35).

The anatomical composition of the human groin make this area especially exposed to bulging of intraabdominal content. Groin hernias occur in the area between the internal oblique muscle, the upper edge of the transverse abdominal muscle, and the lower edge of the superior pubic ramus. This area contains blood vessels and nerves passing from the intraabdominal compartment to the lower extremities. This anatomical space is quite arbitrarily divided into two parts by the inguinal ligament and posteriorly by the fascia transversalis. In the case of failure or weakness of the structures located in this anatomical area, a groin hernia will occur. However, even though the anatomical properties of the human groin makes this area prone to herniation this cannot solely explain the development of groin hernias, since more persons theoretically would develop groin hernias.

#### ***The embryologic aspects of how groin hernias develop***

In the human embryology, the testes originate along the urogenital tract in the retroperitoneum and migrate during the second trimester of the pregnancy to the internal inguinal ring via the processus vaginalis, where the testes arrive after around 6 months of gestation. During the remaining of the gestation period the testes in the male fetus descends through the internal ring of the inguinal canal to the scrotum preceded by - and guided by the processus vaginalis. The development of the processus vaginalis is most likely due to a complex interaction between several factors during the prenatal period, which is controlled by calcitonin gene-related peptide released from the genitofemoral nerve under the

influence of fetal androgen hormones (36,37). At the time of birth, the portion of the processus vaginalis that lies between the testes and the abdominal cavity obliterates, leaving a peritoneal sac that surrounds the testes. The mechanisms behind the obliteration of the process vaginalis are still unknown (38,39). The process is similar in female fetuses, however the processus vaginalis and the round ligament descend into labia majora instead of the scrotum.

In the case that the processus vaginalis does not obliterate or only partly obliterates, a patent processus vaginalis arises, which is considered a main risk factor for indirect inguinal hernia development in children and adults. The right testicle will normally descent slightly later than the left testicle, which could be the reason why a higher number of right-sided hernias is seen, since the right processus vaginalis obliterates later than the left. The final obliteration of the processus vaginalis normally occurs within the first two years of life (40) and the high number of premature infants that develops inguinal hernias emphasizes the importance of the obliteration of the processus vaginalis. Autopsies of newborns have showed that up to 94 % of newborns have patent processus vaginalis (35) and in general, it applies that the earlier the birth, the higher the risk of developing inguinal hernias. Where the cumulative risk of inguinal hernia development in normal term births for boys is around 1% in boys and about 0.1% in girls, it is much higher in premature children at around 7% in boys and about 1% in girls (41–43).

Delayed obliteration of the processus vaginalis is considered one of the main factors for the development of indirect inguinal hernias in infants and adults (16), however it is important to bear in mind that far from all patent processus vaginalis develops into a groin hernia. What exactly that leads a patent processus vaginalis to become a groin hernia is unknown, however it is known that a patent processus vaginalis only has the potential to become a hernia when it is large enough to contain abdominal content. It has been shown that a remarkable large fraction of adults have occult patent processus vaginalis even in the late adulthood, without having clinical signs or symptoms of a groin hernia (44).

#### ***Surgical aspects of groin hernia surgery***

A large number of surgical procedures for groin hernia surgery have been developed through the years. Overall groin hernias can be operated by either anterior or posterior surgical approach. Anterior surgical approaches include open surgical procedures, of which the most commonly performed surgical technique worldwide is the Lichtenstein's technique (45). The basic principle of the Lichtenstein's technique is an opening of the inguinal canal, identifying some or all of the three nerves (iliohypogastric nerve, ilioinguinal nerve, and the genital branch of the genitofemoral nerve), the spermatic cord and vessels, and subsequently the groin hernia. A mesh is inserted after repositioning of the hernia and fixated with sutures to the inguinal ligament and surrounding tissues making sure of overlapping the pubic tubercle medially (46).

The posterior surgical approaches consist mainly of laparoscopic procedures. Two major laparoscopic approaches exist, the transabdominal preperitoneal (TAPP) procedure and the totally extraperitoneal (TEP) procedure. In the TAPP approach a mesh is placed preperitoneally by a peritoneal incision from the abdominal cavity sealing the hernia site internally, while the TEP approach lays the mesh from externally without entering the abdominal cavity sealing the hernia sites externally (47). The mesh is therefore placed in the same anatomical location in the two

procedures. A new “mixed” operation has been described involving an open posterior approach called the ONSTEP procedure, and it uses a horizontal incision more cranially and medially than the Lichtenstein procedure. A mesh is placed preperitoneally medially and between the external and internal oblique aponeurosis laterally (same place as in the Lichtenstein repair) without any external fixation of the mesh (48).

## **METHODOLOGICAL CONSIDERATIONS**

### ***Danish nationwide registers:***

The first of the articles in this thesis (1) made use of a combination of several of the Danish nationwide clinical registers. The Danish Civil Registration System (CRS) was established in 1968, where all people alive and living in Denmark were registered (49). Among many other variables the CRS includes the personal identification number (CRS number), sex, date of birth and continuously updated information on vital status, registration of parents, maternal siblings and potential children. The unique CRS number is used in all Danish national registers enabling linkage between the registers. The Danish National Hospital Register (NHR) registers all elective, acute and outpatient treatments in private and public hospitals as well as surgical procedures performed in Denmark (50). This registration began in 1977 with all elective and emergency hospital admissions and/or procedures, and in 1995 outpatient contacts and emergency contacts were added to the registration.

Our study combined data from the CRS with data from the NHR. A nationwide population covering all Danish citizens alive and living in Denmark was drawn from the CRS. This data were combined with knowledge of groin hernia operations (inguinal hernia and femoral hernia) from the NHR to establish the cohort of interest using the 10th edition of the International Classification of Diseases (ICD-10). The study period covered a five-year interval from January 1st, 2006 to December 31st, 2010.

### ***The Danish Hernia Database:***

Two of the studies used data from the Danish Hernia Database (DHDB) (2,3). The DHDB is a nationwide quality assessment database that started prospectively registering data of groin hernia surgery in 1998 and ventral hernia surgery in 2005 (51). The DHDB registers all groin hernia procedures performed in Denmark in adults (> 18 years) and are including details on anesthesia, type of hernia, type of procedure (primary or recurrent), type of surgical procedure and type of mesh (52). The operating surgeon records the details immediately after the procedure. The completeness of the procedures registered in the DHDB compared with the number of procedures being performed yearly (controlled via the NHR) have continuously been over 90 %, however the precise completeness vary yearly (53).

### ***Systematic review and meta-analysis***

A systematic review is generally performed to assess the findings in a number of studies addressing the same or aspects of the same topic in order to strengthen the evidence in that research area and aid decision-making. A meta-analysis is the statistical combination of these related findings. For conducting and reporting the systematic review and meta-analysis (4) we used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline and checklist (54,55), as well as the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guideline (56) whenever applicable. Both of these guidelines

contains detailed reporting checklists, which authors can adhere in order to correctly and systematically report every aspects of the review to ensure thoroughness and transparency. There is an overlap of the two checklists on several items.

In order to ensure transparency and to avoid unplanned duplication of the review, this review was prospectively registered at the PROSPERO (International Prospective Register of Systematic Reviews) site before the data extraction process was commenced (57). Besides aiding the above-mentioned factors, prospective registration at the PROSPERO site ensures that publication bias is avoided in the event of negative results and reporting bias is revealed in terms of discrepancies between registered and reported literature search, analysis plan, bias evaluation, outcome selection and reported outcome. This should increase the overall quality and credibility of the review. The PROSPERO staff audits registration of the protocol and requests arguments in order to changes an already registered protocol. The registration is expected to be kept up-to-date, and despite several opinion-leaders strongly encourage registration of the review at PROSPERO (58,59), it is still voluntary to register the review.

In order to evaluate the degree of bias of the included non-randomized studies and to overall estimate the general quality of the results drawn from the review, we used two different methods of evaluation. The Newcastle-Ottawa Scale (NOS) was used to evaluate the degree of bias and quality on study level (60,61). The NOS uses a “star-based” system that grades the specific studies according to selection of participants (maximum of four stars), comparability of study groups (maximum of two stars) and outcome assessment (maximum of three stars). To ease the interpretation of the NOS score the scores were compiled for each study, and a score of 0-3 indicated high risk of bias, 4-6 a moderate risk of bias and 7-9 a low risk of bias.

In order to evaluate the overall quality of the meta-analysis outcomes we used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (62). The GRADE approach uses several factors that can downgrade or upgrade the overall quality estimate. Among the downgrading factors are a moderate or high risk of bias (compiled NOS score <4 or < 7, respectively), high degree of inconsistency (heterogeneity > 50 % measured by the I2 statistics), indirectness, imprecision of the effect estimate, and publication bias (visualized from the funnel plot). The upgrading factors are large or very large effect estimates (RR > 2 or RR>5, respectively), confounding changes of the effect estimate that lowers the effect estimate and occurrence of a dose response gradient. For evaluating the outcome we used the GRADE profiler assessment tool (GRADE-pro vers. 3.2), as recommended by the Cochrane Collaboration (61).

### ***Statistical considerations related to the database studies:***

In the register-based study combining the CRS and NHR registers to estimate the nationwide occurrence of groin hernia surgery (1), data were presented as the raw number of procedures as well as by the age-adjusted prevalence. We chose methodologically that each person could only appear one time in each of the hernia categories not matter the possible number of hernia procedures performed in the study period. The prevalence estimate simply describes the number of cases with the outcome (i.e. groin hernia surgery) divided by the total number of persons in the cohort. The age-adjusted prevalence estimates were calculated as the number of people operated on for inguinal or femoral hernia in the five-year interval during the study period, divided by the number of citizens living in Denmark on December 31st, 2010 in the same

age interval, with regard to that one individual could only count once. The age-adjusted prevalence estimates indicated the percentage of people with the outcome of the corresponding age group of the population that at a given time during the five-year period had an inguinal or femoral hernia repair performed. These analyses were stratified by gender. The 95 percent likelihood ratio based confidence limits for the five-year prevalence was estimated by binomial regression (63).

In the two studies investigating groin hernia recurrences in relation to gender and hernia subtype (2,3) several different statistical methods were used. In order to describe the correlation between the type of hernia at primary and recurrent procedure, a first order semi-partial correlation test was chosen. The reason we chose a partial correlation test over other correlation tests (i.e. Pearson's test, Spearman's test, Kendall's tau or biserial correlations) was the ability of controlling the effect of additional variables while estimating the correlation. That the correlation was "first-order" meant that we controlled the effect of one factor in the analysis (i.e. the type of repair at the primary operation). That the correlation was "semi-partial" meant, that the relationship between the hernia type at primary and recurrent procedure was quantified, while controlling the effects of the type of repair at only the primary procedure. This was chosen since the type of repair at the primary procedure could not affect the type of hernia at that same primary procedure. A semi-partial correlation is different to a partial correlation, which controls the effect of a factor (ex. the type of repair at the primary procedure) on both correlation variables (64).

In order to estimate the relative risk of reoperation based on the specific inguinal hernia subtypes (2,3), we used Cox proportional hazards regression model. The event was binary defined as inguinal hernia reoperation (yes/no) and we controlled the relative hazards estimates for possible important covariates (year of repair, age, type of repair). The Cox proportional hazards model is a semi-parametric survival analysis that assumes that the hazard ratio of event is proportional (time-independent) during the observation period. It is not an assumption that the hazard-rates are equal over time, just that the hazard ratios are constant. We used a time-constant Cox regression model (enter model instead of forward or backward model) in opposed to a time-dependent Cox regression model where the relative hazard of the event changes over time.

For evaluating reoperation rates for indirect inguinal hernias operated by laparoscopic technique during the study period (2), we used Kaplan-Meier non-parametric survival analysis and one-minus survival plots to depict the cumulative failure rates (reoperation). The Kaplan-Meier analysis is not designed to assess the effect of covariates, as it is a descriptive analysis for time-to-event variables. We used the Log-rank test (also known as the Mantel-Cox test) for establishing significance. The Log-rank test does not supply risk estimates, only levels of significance between the tested groups. The Kaplan-Meier analysis and the Log-rank test assume that the probability of event depends only on time, that no change in effectiveness of the treatment is present over time, and that censored patients have the same probability of event as those fully followed up.

#### **Statistical considerations related to the meta-analysis:**

Studies that are brought together in reviews addressing a specified research question will inevitably differ from one another with a degree of diversity. This can be due to clinical, methodological or statistical differences among the included studies. In meta-analyses this difference is often called heterogeneity. Statistical

heterogeneity arises when the observed intervention/outcome effects from the included studies are more different, that would be expected from random chance alone (65). Clinical differences can lead to statistical heterogeneity if the intervention or outcome is affected by factors that vary across studies (i.e. different patient characteristics or if different interventions are used in the included studies). Methodological differences can lead to heterogeneity if outcomes are defined or measured differently between the studies, and will suggest that the studies are subject to different degrees of bias. Assessment of heterogeneity in meta-analyses is important, as the generalizability of the results can be compromised if the results are prone to inconsistency.

It has been argued that some degree of statistical heterogeneity always will exist in meta-analyses whether it can be detected by statistical tests or not (66). It all depends on how heterogeneity is measured and quantified, as this can be done in several different ways. Visually, a lacking overlap in the forest plot of the horizontal lines representing confidence intervals of the included studies will indicate some degree of heterogeneity. The Cochran's Q-statistic and the Chi2 -test that are included in forest plots assesses whether the differences are compatible with chance alone (a low p-value indicates heterogeneity). The Chi2 -test should be interpreted with caution in cases with a low number of studies in the meta-analysis, since heterogeneity in these cases can be present without Chi2 being significant ( $p < 0.05$ ). In the case of many included studies in a meta-analysis, the test will be able to detect heterogeneity that may not be clinically relevant. Therefore, it can be difficult to interpret the importance and impact of the heterogeneity measured by the Q-statistics or Chi2 test. Another measure of the importance of the heterogeneity has been developed, called inconsistency (I<sup>2</sup>). The I<sup>2</sup>-measure quantifies the degree of variability among the included studies by the use of the Chi2-statistics (Q) and the degrees of freedom (df) (dependent of the number of included studies in the meta-analysis) from the pooled estimate, in order to provide a more easy interpretable value. The I<sup>2</sup>-measure range from 0-100 %, and is easily interpretable since 0 % indicates no heterogeneity and 100 % indicates complete heterogeneity (66,67). We considered heterogeneity as high when I<sup>2</sup> > 50 % (with respect to downgrading the quality estimate in the GRADE analysis) and heterogeneity as being substantial when I<sup>2</sup> > 75 % (with respect to not presenting the graphical pooled effect estimate) (65).

When performing a meta-analysis methodological choices have to be made. We used the inverse-variance method for typing in data, which assigns the relative weight to each study according to the inverse variance (one over the square of the standard error) (68). When performing a meta-analysis on dichotomous outcomes either a fixed-effects model or a random-effects model can be used, and no final guideline can be obtained whether to use one or the other. The random-effects model is often used when it cannot be assumed that all studies are estimating the same underlying value and sees the differences as being random according to a normal distribution (68). The center of the pooled effect describes the average of the effect and the confidence interval describes the uncertainty of the mean. In the random-effects model the standard errors of the included studies are adjusted to the amount of heterogeneity, while the fixed-effects model uses the assumption that the true effect of the intervention is the same in every study that assesses the outcome (i.e. the effect is fixed). This assumption implies that any observed differences in the study results are strictly due to chance. In the case of heterogeneity that is believed to be the result from clinical diversity, the random-effects model addresses the average

effect of the measured outcome, while the fixed-effects model addresses the best estimate of the outcome. In cases of no heterogeneity the two models produce identical pooled estimates.

For detecting publication bias (small studies with negative results not being published) we used funnel plots where possible publications bias was visualized by plotting the inverse variance of the studies (surrogate measure for study size) by the study effect. In the case of no publication bias, the plot will be symmetrical about the pooled value for the included studies. However, many other factors than publication bias can lead to asymmetry of a funnel plot including language bias, data irregularities (poor methodology, analysis strategy, fraud), and chance (69).

## STUDY PRESENTATION

### STUDY 1: NATIONWIDE PREVALENCE OF GROIN HERNIA REPAIR *Objective*

The objective of this study (1) was to provide an epidemiologic overview of the groin hernia operations on a nationwide basis by estimating the age- and gender-specific prevalence of inguinal and femoral hernias.

### *Methods*

A five-year nationwide cohort was constructed using the Civil Registration System (CRS) covering all Danish citizens from year 2007-2012. Within that cohort we analyzed all inguinal and femoral hernia operations during the study period using the IDC-10 groin hernia operation codes derived from the National Hospital Registry (NHR) (Table 1). We stratified all inguinal hernia and femoral hernia operations into gender and age specific groups. Cases were excluded from occurring more than once in each hernia category (inguinal and femoral hernia) in order to minimize the number of recurrent procedures. Numbers were presented as age-adjusted prevalence and raw numbers.

### *Results*

We included a total of 46,717 persons operated for a groin hernia from the population of 5,639,885 people (2,799,105 males, 2,008,780 females). We found that 97 % of all groin hernia repairs were inguinal hernias and 3 % femoral hernias. We saw a bimodal distribution of inguinal hernia repair with peaks in childhood and among the elderly for both genders (Figure 1, Figure 3). More males than females had inguinal hernia repairs. Among femoral hernias we found that a steadily increasing number of procedures were performed in both males and females throughout life (Figure 2, Figure 4). More females than males had femoral hernia repairs.

### *Conclusion*

We found that the gender stratified age distribution of inguinal and femoral hernias varied very differently. For inguinal hernias a bimodal distribution with peaks in childhood and among elderly was seen more significantly for males than females, whereas for femoral hernias a steadily increasing number of procedures was seen throughout life. The study generated the hypothesis that the disease etiology for inguinal and femoral hernias very different, however also that a difference between the inguinal hernia subtypes existed – that idea was generated on the basis of the age-curves.

### *Strengths and Limitations*

In this study several limitations and weaknesses were embedded. Our estimation of the operation rate was only an approximation of the true groin hernia prevalence. Part of the underestimation was due to the exclusive use of operation codes (i.e. no diagnosis-codes were used), which eliminated all patients diagnosed with a hernia, but not operated for their hernia. Another part of the underestimation was the exclusion of persons from appearing more than one time in each of the hernia categories (inguinal hernia, femoral hernia), which was a surrogate measure for primary hernia development. Since the main focus of this article was to provide a stratified overview of the distribution of inguinal and femoral hernias, and not to perform a socioeconomic evaluation of the disease burden of groin hernias, we chose this model. Therefore, we cannot be sure that the prevalence estimates depicted in this investigation is of primary hernias is that we have no knowledge of potential hernia surgery before the study. It was not possible to calculate incidence estimates since we could not rule out the fact that the included persons had been groin hernia operated before.

A potential limitation of this study was the use of data from the NHR. In the NHR it is unfortunately not possible to withdraw data on the subtype of inguinal hernia or the mode of admission (emergency versus elective). Even though the NHR contains strength due to the large amount of data it contains, the data is only as complete and valid as the data registered into the database from the departments. A formal audit of the groin hernia data in the NHR has not been performed with regard to completeness or accuracy. However, surgical departments and private hospitals have a vested interest in entering data in correctly and in proper time, since the NHR forms the basis of economic reimbursement. Furthermore, the NHR data completeness has been validated for numerous other operations and diagnoses and in 2008, the National Board of Health estimated that only 5% of all operations were missing from the NHR (70). As in all prevalence studies (point prevalence or periodic prevalence studies) it is important that everyone in the population (i.e. the group represented by the denominator) must have the potential to enter the group represented by the outcome (i.e. the nominator). This criteria was also fulfilled in our study, however it differed from other studies by the fact that persons could only count one time in each hernia group. It should be noted that the English terminology regarding the Danish "Lands Patient Register" (LPR), which is managed by the Danish Health and Medicines Authority (71), in publications are referred to as the Danish National Hospital Register (DNHR/NHR) (50), the Danish National Patient Register (NPR) (70), and the Danish National Health Registry (DNHR) (72). However, all of the terms are referring to the same nationwide registry.

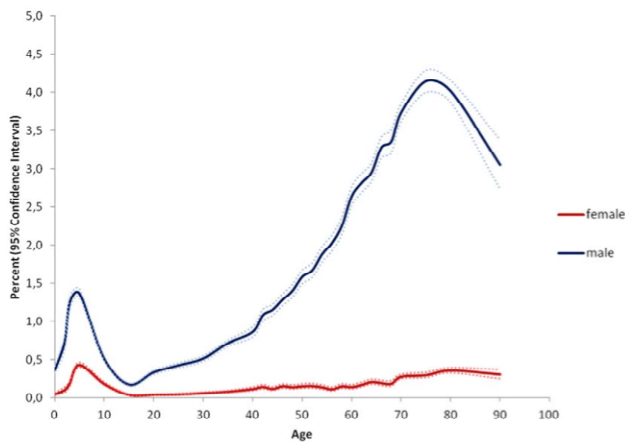
On the positive side this study represents the largest study on the area and the only nationwide epidemiologic study of groin hernias surgery in the literature. By the use of operation codes we focused on people that benefited from treatment (i.e. the persons that were operated for a groin hernia) (73). Due to the design of the study (a prevalence cohort study), it was not possible for us to estimate the lifetime risk of developing a groin hernia since this presupposes incidence data.

### Table 1

Inguinal hernia repair	Females	Males	Total
	<b>4,455</b>	<b>41,109</b>	<b>45,564</b>
KJAB00 (unspecified)	1,362	5,262	6,624
KJAB10 (plasty)	144	648	792
KJAB11 (laparoscopic)	921	6,375	7,296
KJAB20 (fascia transplant)	5	19	24
KJAB30 (mesh)	1,940	28,517	30,457
KJAB40 (plasty through laparotomy)	11	34	45
KJAB96 (other type)	53	121	174
KJAB97 (laparoscopic other type)	19	133	152
<b>Femoral hernia repair</b>	<b>992</b>	<b>421</b>	<b>1,413</b>
KJAC10 (unspecified)	316	124	440
KJAC11 (laparoscopic)	216	109	325
KJAC30 (mesh)	355	144	499
KJAC40 (plasty through laparotomy)	39	15	54
KJAC96 (other type)	60	24	84
KJAC97 (laparoscopic other type)	6	5	11

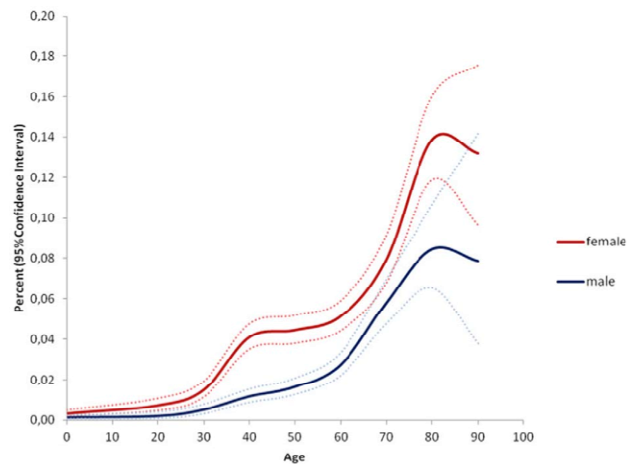
Surgical characteristics of the inguinal and femoral hernia procedures. Both the Danish ICD-10 operative codes and a brief description of the procedures are mentioned. Reprinted from (1).

Figure 1



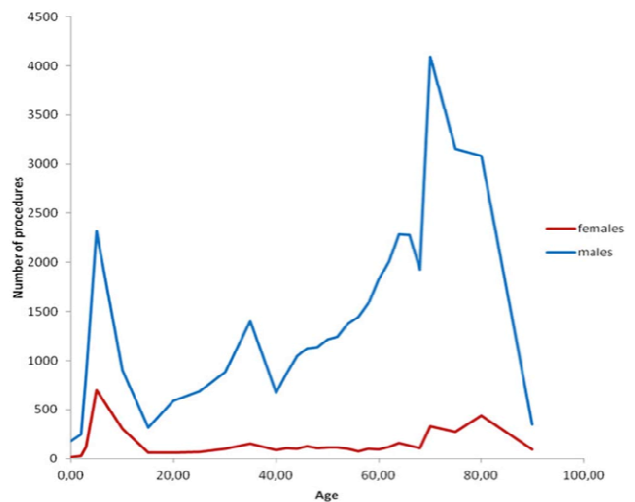
Prevalence of inguinal hernia repair stratified by age and gender. The results indicate the percentage of persons at a given age in the population who were operated for an inguinal hernia during the study period. Example: 4.14% CI 4.0–4.29% of all males aged 75–80 years in Denmark were operated for an inguinal hernia at least once during the study period. Reprinted from (1).

Figure 2



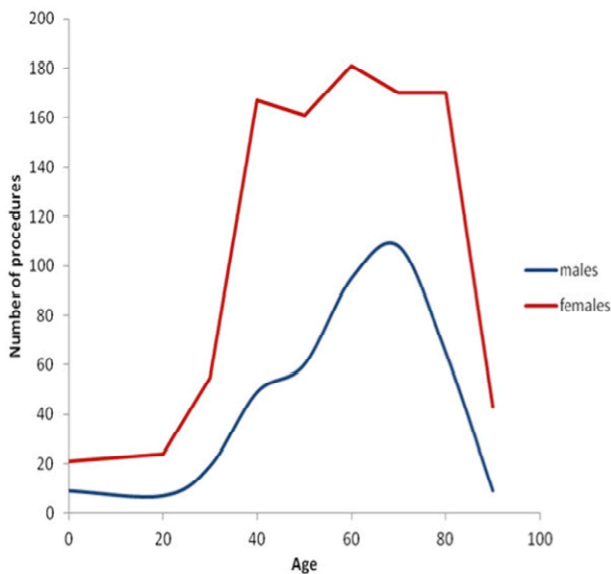
Prevalence of femoral hernia repair stratified by age and gender. The results indicate the percentage of persons at a given age in the population who were operated for a femoral hernia during the study period. Example: 0.14% CI 0.12–0.16% of all females aged 80–90 years in Denmark were operated for a femoral hernia at least once during the study period. Reprinted from (1).

Figure 3



Numerical number of inguinal hernia repairs performed stratified by age and gender. Reprinted from (1).

Figure 4



Numerical number of femoral hernia repairs performed stratified by age and gender. Reprinted from (1).

## STUDY 2: RECURRENCE PATTERNS OF DIRECT INGUINAL HERNIAS AND IN DIRECT INGUINAL HERNIAS IN A NATIONWIDE POPULATION IN DENMARK

### Objective

The objective of this study (2) was in a male nationwide population to determine the risk of reoperation of the subtypes of inguinal hernia and determine the type of recurrence by the subtype of inguinal hernia.

### Methods

By using data from the Danish hernia database (DHDB) a cohort covering 14 years was constructed including all male patients electively operated for a primary inguinal hernia (direct or indirect inguinal hernias) by Lichtenstein's technique or laparoscopic technique. In this prospectively gathered cohort we registered type of hernia at the primary and recurrent operations (direct or indirect inguinal hernias), the number of recurrences and the type of repair (Lichtenstein or laparoscopic). In order to evaluate the risk of reoperation based on the hernia subtype at the primary procedure we performed multivariate adjusted Cox regression as well as first-order semi-partial correlation analysis.

### Results

A total of 85,314 males were included in the study-cohort. A total of  $n=75,404$  (88 %) of the patients were operated by Lichtenstein's technique and  $n=9,910$  (12 %) were operated laparoscopically (97.2 % TAPP, 2.8 % TEP). The overall inguinal hernia reoperation rate was 3.8%, and subdivided into indirect inguinal hernias and direct inguinal hernias, the reoperation rates were 2.7 % and 5.2 %, respectively ( $p<0.001$ , Chi-square). In the multivariate Cox proportional hazards analysis of factors predicting reoperation, we found that a direct inguinal hernia at primary operation was a substantial risk factor for recurrence with a Haz-

ard ratio of 1,90 (CI 95% 1.77 – 2.04) compared with an indirect inguinal hernia at primary operation ( $p<0.001$ ). Laparoscopic repair was a slight risk factor for recurrence with a Hazard ratio of 1.07 (CI 95% 1.01-1.13). We found that there was a significant relationship between the type of hernia at the primary operation and reoperation, when controlling for the effect of the operation method,  $r=0.45$  ( $p<0.001$ ). This corresponded to an odds ratio (OR) of 7.1 (CI 95% 6.0-8.4) of being reoperated for a direct inguinal hernia, and an OR of 3.0 (CI 95% 2.7-3.3) of being reoperated for an indirect inguinal hernia if the primary operation was for an indirect inguinal hernia (Table 2). As subsequent findings, we saw that the frequency of laparoscopic hernia repair increased during the study period and that the laparoscopic repair of indirect inguinal hernias recurred more often than indirect inguinal hernias operated by Lichtenstein's technique ( $p<0.001$ ).

### Conclusion

We found that the overall reoperation rate was significantly higher after primary operation for direct inguinal hernias compared with indirect inguinal hernias. Furthermore, we found a significant correlation between the type of inguinal hernia at the primary and recurrent procedures.

### Strengths and limitations

A limitation in this study was the use of reoperation rates as a surrogate measure for the recurrence rates. It is known that the reoperation rate underestimates the true recurrence rate by approximately 40 % (23), due to surgery indications or lack of contact to the healthcare system. Even though the DHDB has been proven in a position to deliver valid data with regard to quantity and quality multiple times, some limitations and restrictions adhere to the DHDB. The DHDB did not register all groin hernia operations performed by surgeons in private practice in the beginning of the registration period, and even though the surgeons in private practice only perform a minimal amount of groin hernia procedures, this fact reduces the overall nationwide data completeness. Furthermore, data from the DHDB do not include postoperative follow-up or access to valid information regarding the operating surgeon (i.e. experience). This information can only be extracted from the DHDB for local internal audit on department level. With regard to the possible nationwide learning curve of laparoscopic groin hernia surgery, it is likely that a limited number of experienced hernia surgeons operated laparoscopically in the beginning of the DHDB registration period. During the DHDB registration period this technique has been dramatically spread out on more perhaps inexperienced hands, which can have affected the overall recurrence rates data on a national level.

Even though we used data from a nationwide prospectively recorded cohort, several restrictions were applied which potentially can result in limitations. We restricted the group of interest by the type of hernia (only inguinal hernias) and the operation method (only Lichtenstein's technique or laparoscopic repair) in order to homogenize the group. This was done to reduce the possible confounding effects on recurrence rates from lesser commonly used operation types. This study made use of a long follow-up period, which increased the possibility of detecting recurrences.

Several epidemiologic methods were applied in this study. All persons not reoperated at the end of the study period were right censored (i.e. possible reoperations had yet to come beyond the study period). Furthermore, this study made use of left truncation



(i.e. patients entered the study at random times in the study period upon operation and were followed from this delayed entry time until the event occurred or until the subject was right censored). We could not correct for potential right-truncated cases (persons leaving before potential reoperation occurred). We used a multivariate survival analysis model (Cox proportional hazards model) where it was possible to control the effect of the estimate by the year of operation, the age and at the type of repair, which improved and strengthened the message of the paper. The fact that we also could adjust for the effect of repair method in the correlation analysis was considered to be a strength in this study. That said, it should be mentioned that an adjusted positive correlation does not state anything regarding causality. In this study both the time-course (i.e. time to reoperation) of recurrences and the outcome (i.e. crude reoperation rates based on hernia type at primary operation) were of interest. The use of the Cox proportional hazards model assumes that the distribution of right-truncated cases between the groups is equal, which was not possible to investigate. This could result in bias if this distribution was different. However, we have no reason to believe that a specific hernia type should lead to non-random right-truncation.

**Table 2**

	Primary procedure DIH	Primary procedure IIH	Total
<b>Total</b>	1,923	1,304	3,227
<b>Inguinal hernia</b>	1,786 (92.9 %)	1,230 (94.3 %)	3,016 (93.5 %)
DIH	1,301 (72.8 %)	382 (31.1 %)	1,683 (55.8 %)
IIH	380 (21.3 %)	792 (64.5 %)	1,172 (38.9 %)
Pantaloon inguinal hernia or not specified	105 (5.9 %)	56 (4.4 %)	161 (5.3 %)
<b>Femoral hernia</b>	83 (4.3 %)	43 (3.3 %)	126 (3.9 %)
<b>Combination hernia</b>	26 (1.4 %)	5 (0.4 %)	31 (0.9 %)
<b>No hernia</b>	28 (1.4 %)	26 (2.0 %)	54 (1.7 %)

Operative findings at reoperation. DIH: direct inguinal hernia, IIH: indirect inguinal hernia.

### STUDY 3: DIRECT INGUINAL HERNIAS AND ANTERIOR SURGICAL APPROACH ARE RISK FACTORS FOR FEMALE INGUINAL HERNIA RECURRENCES

#### Objective

The objective of this study (3), was to determine the risk of reoperation based on the different subtypes of inguinal hernias and establish the correlation between the type of recurrent inguinal hernias to the type of primary inguinal hernias in females.

#### Methods

Data were obtained from the Danish hernia database (DHDB) over a 14-year period from 1998 to 2012. We chose all electively operated primary inguinal hernias repaired by Lichtenstein's technique or laparoscopy. Within this percent prospectively gathered cohort we registered the type of hernia at the primary procedure (direct inguinal hernias or indirect inguinal hernias) and recurrent procedures (femoral hernias, direct inguinal hernias, indirect inguinal hernias), the type of repair, and number of recurrences. We analyzed data using multivariate the Cox proportional hazards model as well as first-order semi-partial correlation analysis.

### Results

A total of 5,893 females had primary elective inguinal hernias operated in the study period (61 % indirect inguinal hernias (IIH), 37 % direct inguinal hernias (DIH), 2 % combined DIH+IIH). Of those, a total of 305 operations for recurrences were registered (61 % inguinal recurrences, 38 % femoral recurrences, 1 % no hernia), which corresponded to an overall crude reoperation rate of 5.2 % (Table 3). A noticeable difference was found in reoperation rates after primary operation for DIH, IIH and combined DIH+IIH of 11.0 %, 3.0 % and 0.007 %, respectively ( $p < 0.001$ , Chi-square) (Table 3). In the multivariate Cox proportional hazards analysis of factors predicting reoperation, we found that a direct inguinal hernia at primary operation was a substantial risk factor for recurrence with a Hazard ratio of 3.1 (CI 95% 2.4 – 3.9) compared with an indirect inguinal hernia at primary operation ( $p < 0.001$ ). Laparoscopic operation was found to give a lower risk of recurrence with a Hazard ratio of 0.57 (CI 95% 0.43-0.75) compared with Lichtenstein's technique ( $p < 0.001$ ). The year of operation did not influence the risk of recurrence ( $p = 0.845$ ), neither did the anesthesia method ( $p = 0.693$ ), whereas a lower age carried a slightly lower risk for recurrence with a Hazard ratio of 0.99 (CI 95% 0.98-0.99) ( $p = 0.003$ ). We found that patients operated for a primary DIH had an increased risk of femoral recurrence compared with primary operation for an IIH with a Hazard ratio of 2.4 (CI 95% 1.7-3.5) ( $p < 0.001$ ). We did not find any significant correlation between the type of primary and recurrent hernia since recurrences tended to be direct inguinal hernias no matter the type of hernia at the primary procedure. As a subsequent finding we found that all of the femoral recurrences ( $n = 116$ ) occurred after Lichtenstein's procedure and none occurred after laparoscopic operation ( $p < 0.001$ , Log Rank test). Lichtenstein's procedure was not just a risk factor for femoral recurrence but also for inguinal hernia recurrences since 3.9 % of inguinal recurrences occurred after Lichtenstein's repair and 1.2 % of inguinal recurrences occurred after laparoscopic repair ( $p < 0.001$ , Chi square).

### Conclusion

Elective direct inguinal hernias in females recurred three times as often as indirect inguinal hernias. We found that the recurrent hernias tended to be direct no matter of the type of primary inguinal hernias repaired. Femoral hernias only recurred after anterior surgical repair at the primary procedure and furthermore, we found that femoral recurrences was correlated to primary operation for DIH when controlling for the effects of the surgical procedure.

### Strengths and limitations

As a limitation of this study was the fact, that we used reoperation as a proxy for recurrence, since it has been shown that reoperation rates are up to 40 % lower than recurrence rates (23). Furthermore, several restriction were imposed the cohort which potentially can constitute limitations. We excluded femoral hernias as primary procedures, which in females comprise a larger part of the groin hernia operations than in males. The reason for this restriction was an effort to homogenize the population, since femoral hernias for a large part are operated as emergency procedures (74,75) and was operated using a variety of different surgical techniques (76). If we had included primary femoral hernias; we would have had to compromise the choice to only include persons operated by the commonly used techniques (Lichtenstein's technique or laparoscopy).

As for the other of the recurrence DHDB studies in males (2), this study made use of right-censoring cases not yet recorded



with the outcome of interest (i.e. reoperation) at the end of the study period. Furthermore, cases in this study cohort were left truncated (i.e. patients entered the study cohort at random times during the study period and were followed until outcome of interest or right-censoring). As for the other recurrence study, the use of the multivariate Cox proportional hazards survival analysis increased the chance of providing estimates that were controlled for the effects of correctable confounders. However, also in this study did the assumption apply of equal distribution of right-truncation between the groups. We could not control for or analyze the distribution or amount of persons that were right truncated during the study period, however we have no reason to believe that the hernia type should influence the distribution of right-truncation.

On the positive side this is the largest first nationwide correlation register study using data from a reliable high rate database which has been validated several times before. The fact that we used nationwide registers, it eliminated single surgeon bias and possible center bias. Furthermore, we used a long follow-up period, which should maximize the chances of the detecting reoperations.

#### **STUDY 4: PATIENT RELATED RISK FACTORS FOR RECURRENCES AFTER INGUINAL HERNIA SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES**

##### **Objective**

The objective of this study (4) was to quantify the existing evidence on the non-technical patient-related risk factors for recurrence after inguinal hernia repair.

##### **Methods**

This review and meta-analysis was performed according to the PRISMA and MOOSE guidelines. Prior to data extraction the review was registered at the PROSPERO register. A literature search was performed in March 2013 in the MEDLINE, Embase and Cochrane CENTRAL databases including the search words: inguinal hernia, recurrence, reoperation, second-look and risk factors (Figure 5). Only non-randomized observational studies evaluating patient-related risk factors for recurrence after inguinal hernia repair were included. Meta-analysis was performed whenever comparable outcomes made it possible. The Newcastle Ottawa scale was used to quantify the risk of bias on study level, whereas the GRADE approach was used to estimate the overall quality of the study outcomes. We used the random effects model to yield pooled effect estimates. The results from the meta-analyses were presented as forest plots which depicts the estimate of each study as a square and horizontal lines to indicate the 95 % confidence interval for the estimates. The overall pooled values with the combined 95 % confidence interval were shown at the bottom of the graphs.

##### **Results**

From a total of 5,061 records screened, we included a total of 40 observational studies enrolling 720,651 inguinal hernia procedures in 714,917 patients. A total of 14 studies were included in a total of 7 meta-analyses covering a total of 378,824 procedures in 375,620 patients (Figure 6). A total of 27 patient-related risk factors after inguinal hernia repair were included in this systematic review. Of those were eight variables included in meta-analyses (gender, age, hernia subtype, hernia size, reoperation versus primary operation, bilateral occurrence, mode of admis-

sion, and smoking). The patient-related factors related to higher risk of recurrence after inguinal hernia surgery were female gender (RR 1.38, 95 % CI 1.28 – 1.48, I<sup>2</sup> = 0 %), direct inguinal hernia at primary procedure (RR 1.91, 95 % CI 1.62-2.26, I<sup>2</sup> = 10 %), operation for a recurrent inguinal hernia (RR 2.2, 95 % CI 2.0-2.42, I<sup>2</sup> = 6 %), and smoking (OR 2.53, 95 % CI 1.43-4.47, I<sup>2</sup> = 0 %). Furthermore, we found that emergency admission; connective tissue composition and degradation; and positive family history had an impact on the risk of recurrence, while post-operative convalescence and age had no impact on the risk of recurrence.

##### **Conclusion**

In conclusion, we found that female gender; direct inguinal hernias; recurrent hernias; and smoking were risk factors for recurrence after inguinal hernia surgery. Non-technical patient-related risk factors for recurrence should be taken into account in clinical practice as well in the design of future studies of inguinal hernia surgery.

##### **Strengths and limitations**

One of the main potential limitations of any systematic review is the search strategy, which also applies in this review. Even though the search strategy was performed in several of the largest most relevant databases with very wide non-limiting search terms and supplied with reference list searches from the included studies, it cannot be eliminated that potentially relevant studies were missed. We only included studies published in English, which potentially is a limitation of the study (i.e. language bias). However, it has been shown that even though some studies may be overlooked by only including studies published in English, the overall effect of excluding non-English language studies was very limited (77). The fact that we only included non-randomized observational studies could be considered as a limitation of the study due to the increased risk of bias of the included studies. However, it is not possible to randomize patients to patient-related risk factors (ex. gender, age, hernia-type etc.), and a meta-analysis considering these factors therefore must be based on descriptive studies. We chose to include both comparative and non-comparative observational studies in the review, which made the study more heterogenic than, if we had focused on one design.

The systematic review and meta-analysis was conducted using the present the guidelines for this type of study i.e. PRISMA and MOOSE (54–56) and furthermore it was prospectively registered at PROSPERO (57). The compliance of these guidelines adds strength to the study due to the systematic and thorough approach they provide in the conduction and reporting of the review. We used the Newcastle-Ottawa Scale (NOS) to evaluate the degree of bias on study level (60), however it has been shown that the NOS scoring reliability is low between reviewers, and criticism of the NOS scoring system exist (78,79). In our review two reviewers NOS scored the included studies and settled differences by discussion. Unfortunately, we did not perform comparative statistics on the degree of disagreement. The GRADE approach was used to evaluate the quality of the outcomes estimates, and especially the combination of the GRADE and NOS is considered a possible strength in this particular study.

Advantages of meta-analysis include the ability to generalize data from individual studies with a greater number of studied subjects, higher statistical power, and being able to control for between-study variations and to show indications of possible publication bias exists. However, meta-analysis does have certain disadvantages. A disadvantage includes the fact that the study is

based on published data, which are not controlled by this analysis. The fact that we used the random-effects model to compare data, imply that potentially disparate results have been combined into summary estimates (80) and meta-analyses of observational data have been criticized to produce precise-looking estimates of weak effects (81). On the positive side this systematic review and meta-analysis is the first of its kind in this research field and it represents a very large patient material due to the included register-based studies from the Swedish Hernia Registry (SHR) and the DHDB.

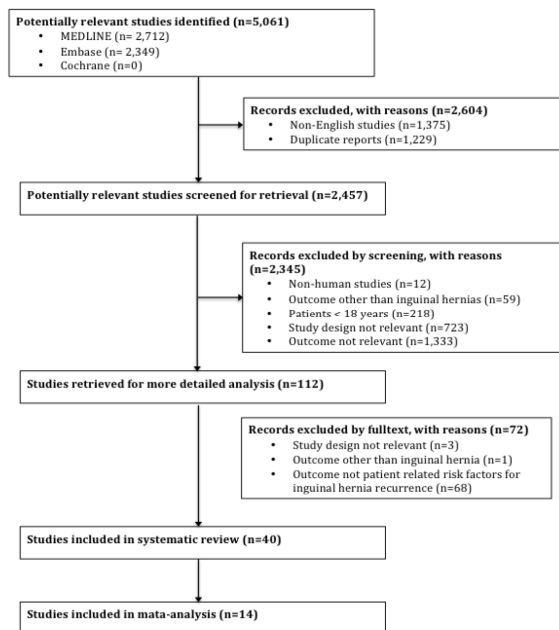
**Figure 5**

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("hernia, inguinal"[MeSH Terms] OR ("hernia"[All Fields] AND "inguinal"[All Fields]) OR "inguinal hernia"[All Fields] OR ("inguinal"[All Fields] AND "hernia"[All Fields])) AND ((second-look surgery"[MeSH Terms] OR "second-look"[All Fields] AND "surgery"[All Fields]) OR "second-look surgery"[All Fields] OR "reoperation"[All Fields] OR "reoperation"[MeSH Terms]) OR ("recurrence"[MeSH Terms] OR "recurrence"[All Fields])
  
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The comprehensive literature search as performed in MEDLINE. The literature search in Embase and Cochrane CENTRAL databases were adapted from this literature search.

**Figure 6**



Flow chart of study selection process.

## DISCUSSION

Several interesting findings were derived from the studies included in this thesis. First, that the gender and age distribution of inguinal hernias and femoral hernias was found to differ distinctly throughout life. Second, that operation for a direct inguinal hernia produced significantly higher recurrence rates in males as well as females compared with operation for an indirect inguinal hernia. Third, that the different subtypes of inguinal hernias were correlated in primary and recurrent operations in males, and fourth, that a number of non-technical patient-related risk factors (including female gender, operation for a direct inguinal hernia, operation for a recurrent hernia, smoking, positive family history and connective tissue composition) significantly influenced the risk of recurrence after inguinal hernia operation.

We found that female gender (3,4), operation for a direct primary hernia (2–4), operation for a recurrent inguinal hernia (4) and smoking (4) were significant risk factors for inguinal hernia recurrences. Why and how any of these risk factors specifically work to produce a higher risk of recurrence is unknown, but could lie in a combination of pathophysiology, pathoanatomy and technical aspects. The reason to why direct inguinal hernias have an increased risk of recurrence could possibly lie in pathophysiology and pathoanatomy since tissue from patients with direct inguinal hernias have been shown to have a distinct changed connective tissue composition compared tissue from patients with indirect inguinal hernias and tissue from healthy controls (82–85). The reason why recurrent inguinal hernias have an increased risk of re-recurrence could be the consequence of many recurrent hernias being direct inguinal hernias, which have a higher risk of recurrence compared to other hernia types (86,87).

The increased risk of recurrence in relation to smoking has been hypothesized to be caused by a changed collagen composition (88,89), most likely due to temporary tissue hypoxia (90). It has also been suggested, that an excessive degradation is induced by smoking due to a higher stimulation of the neutrophil and macrophage response, which has been found to impair wound healing and cause damage to the connective tissue composition and degradation (91). This is in contrast to primary inguinal hernia development, where it has been shown in large epidemiologic studies with multivariate-adjusted analyses that active cigarette smoking actually decreases the risk of inguinal hernia development (29,92).

Regarding the connective tissue composition and risk of recurrence, it has been shown that a distorted pro-collagen I/III ratio (25), collagen I/III ratio (93) and changed levels of MMP-1,13 and TIMP-2 had a significant correlation to the risk of recurrence (26,94). These findings support the fundamental hypothesis of inguinal hernia recurrences being based on a systemic connective tissue failure. A few studies have documented that a positive family history (i.e. directly related first degree family members operated for or diagnosed with an inguinal hernia) is an independent risk factor for early recurrence of inguinal hernias (24,95), however genetic studies investigating characteristics of primary or recurrent inguinal hernias have yet to be published. It has not been shown that physical lifting, short postoperative convalescence, longer postoperative hospital admission or manual labor jobs are significant risk factors for inguinal hernia recurrences (28,96,97). Neither is there any evidence of other diseases (i.e. obstipation, chronic obstructive pulmonary disease, varices, appendectomy and incisional herniation) being related to inguinal hernia recurrences (27,95,98,99). However, the studies relating inguinal hernia recurrences to other diseases have addressed primary inguinal hernias and not recurrent inguinal hernias.

It is still largely unknown why primary or recurrent groin hernias develop. Several theories regarding etiologic reasons for development of primary groin hernias have been published and among those include biomechanical characteristics (100–102), local tissue weakness (103), defect collagen composition (82,104), congenital anatomical factors (44,105–107), and inheritable factors (108). However, the common denominator that could explain causality to why groin hernias arise as frequently as it does is still to be finally clarified. Several hereditary connective tissue based diseases have given indications of a possible underlying pathophysiological mechanism including Ehlers-Danlos Syndrome, Cutis Laxa, Osteogenesis Imperfecta and Marfan's Syndrome (109,110). Via these diseases, disorders in specific connective tissue components including microfibrils, collagen, elastin, and glycosaminogly-

cans have been linked to occurrence and recurrence of groin hernias (111). Other related diseases, which have been hypothesized to relate to the occurrence of inguinal hernias, are abdominal aortic aneurysms (112,113), congenital heart disease (114), and hiatal hernias (29). Furthermore, strenuous physical activity as well as hard physical labor has been found to relate to indirect inguinal hernias but not to direct inguinal hernias (115,116). However, despite the many associations and characteristics the reason to why groin hernias develop or recur is yet to be discovered.

The studies included in this thesis primarily focused on the non-technical risk factors associated with recurrence after inguinal hernia surgery and found that these factors have great impact on the risk of recurrence (2–4). However, despite the importance of non-technical factors in the avoidance of recurrences, the technical surgical aspects surrounding the inguinal hernia surgery must still be addressed. Especially since the technical aspects of groin hernia surgery can be easily implemented and adapted according to new evidence. A meta-analysis found that laparoscopic repair per se produced significantly higher recurrence rates than open repair in primary unilateral inguinal hernias (117). When separated into TAPP and TEP, it appeared that the increased risk of recurrence in laparoscopic hernia repair was correlated to the TEP procedures and not the TAPP procedures. The same analysis found that the perioperative morbidity was elevated in laparoscopic hernia repair, and that this elevation was due to the TAPP procedures and not the TEP procedures. Posterior laparoscopic surgical approaches have been described to be more difficult to learn than anterior open approaches, which is a possible explanation for the higher recurrence rates. It is, however, also possible that technical factors such as e.g. using a too small mesh in the beginning of the laparoscopic era, could explain part of the increased recurrence rates (118). Even though the studies evaluating the learning curve of hernia surgery uses heterogeneous arbitrary outcome measures such as operating time or recurrence rates, some conclusions can be drawn. The learning curve of laparoscopic groin hernia surgery is longer than for open procedures. The TEP procedure is apparently more difficult to learn with operating times stabilizing after 40-100 procedures (119–122) whereas TAPP procedure operating times stabilizing after 30-50 procedures (123,124). A single study examining laparoscopic hernia repair as a whole, found that surgeons who had performed less than 250 laparoscopic hernia procedures had significantly higher recurrence rates than experienced surgeons (16). The learning curve of Lichtenstein's procedure has been estimated to around 40 procedures based on operation time (125).

The above-mentioned meta-analysis did not stratify the results into gender. We found that open repair resulted in significantly higher recurrence rates in females compared to recurrence rates after laparoscopic repair (3). The reason for this could be an incorporated shortcoming of the anterior surgical approach; the possibility of detecting synchronous groin hernias. Others have as us hypothesized that it is due to overlooked femoral hernias at the primary procedure (126–128). This problem is less relevant in males, due to the low frequency of femoral hernias in males. We found that the risk of developing a femoral hernia recurrence in females was absolutely correlated to the use of open surgical repair at the primary procedure. Thus, the problem of femoral hernia recurrences in females is most likely a technical challenge with the surgical method. The DHDB recommends in their newest published guideline that females with groin hernias should be operated by posterior (i.e. laparoscopic) approach (46). Other

technical factors that have been shown to have a significant impact on the risk of recurrence are groin hernia repair using local anesthesia (20,87). Furthermore, the use of non-mesh surgery for groin hernia repair has been proven a significant risk factor for recurrence (129–134) as well as using small meshes (less than 10x15 cm) (135).

It is indisputable that technical factors surrounding the groin hernia surgery have great impact on the risk of recurrence. However, in the recurrence studies included in this thesis (2,3), we adjusted the risk of recurrence by the effect of the type of repair, the time period, the age of the patients, and the method of anesthesia (in females). Even though this adjustment was performed, we still found an independent relation between the type of hernia and the risk of recurrence as well as the type of recurrence. Operation for a direct inguinal hernia has earlier been shown to lead to more reoperations than indirect inguinal hernias both after primary and recurrent procedures in females (20,132). However, the fact that primary operation of a direct inguinal hernia produced higher recurrence rates as well as the fact, that regardless of the subtype of hernia at the primary procedure the recurrent hernia tended to be a direct hernia, is new knowledge. The reason for this is unknown.

In general, large-scale epidemiologic studies can be used to provide an overview of a disease, which can be useful in developing hypotheses. Furthermore, the process of diagnosis and prognosis is based in population data. In groin hernia surgery a limited number of heterogenic large-scale epidemiologic studies exist (136–140). Our study (1) showed that inguinal hernias were more present than femoral hernias in both genders, and that children almost exclusively developed inguinal hernias not femoral hernias. This could imply differentiated disease etiology between childhood inguinal hernias, adult inguinal hernias and femoral hernias. Furthermore, our studies examining recurrences after inguinal hernia surgery (2,3) clearly show that the hernia subtypes in the primary operation has an impact on the type of recurrent hernia as well as the risk of recurrence. It is known that the vast majority of pediatric inguinal hernias are indirect inguinal hernias and most likely a result from a congenital defect closure of the processus vaginalis (107). The underlying mechanisms of a patent processus vaginalis are yet to be resolved, though. As opposed to pediatric inguinal hernias, both direct and indirect inguinal hernias are seen in adults. However, no explanation has so far been given to why direct or indirect hernias develop among elderly persons, why a drastic fall in frequency of inguinal hernia operation during adolescence is seen, and why an increasing frequency of inguinal hernia operation with age occurs. Furthermore, the reason why males numerically account for over 90 % of groin hernia procedures is still unanswered but could be based on inheritable genetic factors. The fact that femoral hernias are practically absent until the mid-twenties, from where the frequency increases for both genders could imply an increasing role of tissue weakness.

One of the major issues in survival data is, that at the time of analysis some patients have not experienced the event of interest (i.e. recurrence in our studies) and furthermore, some patients may be lost to follow-up before the study ends. Both of these types of data lead to censoring of data and bias. Censoring of data means that all information about the data is not fully known (141). All cases in the recurrence studies (2,3) were either uncensored (i.e. reoperation occurring within the observation period) or right-censored (i.e. reoperation not occurred at the end of the study observation time). Since we excluded hernias operated before the DHDB registration period, we also excluded the possi-

bility of left-censoring (i.e. persons with event, however not knowing when exposure to risk started). The possibility of left truncation (i.e. patients being operated and possibly reoperated with no registration of the hernia operation) could be present in the database studies (1–3). A very small fraction of groin hernias are operated in surgical private practices, which did not in the beginning of the DHDB registration period not necessarily report their operations to the DHDB or the NHR. As with censoring of the data, left truncation would lead to bias in the estimates of groin hernia operation rates and reoperation rates (142).

All of the studies included in this thesis have used reoperation as a surrogate measure for recurrence. This method is by far the most valid measure of recurrence since inter-observer uncertainty is embedded in clinical groin hernia diagnosis, which is avoided by using reoperation as a measure. However, the use of reoperation as a proxy for recurrence gives a conservative estimate of the real recurrence rate since not all patients are eligible for reoperation or should be reoperated for their recurrence and due to the fact that reoperation rates underestimates the true recurrence rate by approximately 40 % (23). For persons to be operated signs and symptoms have to be present, medical care has to be sought, a diagnosis must be confirmed and valid indications for operation must be present. Patients with groin hernias can drop out in each of these steps. By using reoperation instead of clinical diagnosis we measured the epidemiology of indications (i.e. patients expected to benefit from surgical treatment) (73). However, in the older part of the population where we saw that the operation rate was very low (1), reoperation as a measure for occurrence or recurrence of inguinal hernias could lead to a large underestimation due to conservative operative indications.

A possible cause of underestimation of the recurrence estimates in the DHDB studies (2,3) is that childhood hernia operations are not registered in the database. Even though the surgeon registers the type of procedure (primary or recurrent) in the DHDB, it introduces the risk of bias due to left truncation. Persons operated for a childhood groin hernia and reoperated for a recurrence as adults are therefore not included in our analyses, and our recurrence estimates therefore represent an underestimation. Another limitation of the DHDB is the lack of physical follow-up within the DHDB structure. Because cohort studies often have to involve long-term follow-up, require a large number of participants, and require maintaining contact with subjects especially when dealing with a disease that can recur as late as ten years after primary repair. These classical problems of a cohort study were not applicable in this study due to the nature of the DHDB database structure. A possible limitation of a quality database such as the DHDB is the degree of surveillance by which data are entered. The DHDB is subject to passive surveillance, meaning that completeness and quality of data relies on surgeons that are requested or mandated to enter data in addition to other tasks without receiving additional funds or resources. As a result there are increased risk of underreporting and lack of completeness compared with active surveillance, where dedicated project staff are responsible for entering data. A strength of a database such as the DHDB, is the large amount of data and the long follow-up of participants. The large amount of data contained in the DHDB allows small absolute differences to be investigated and increases the overall external validity of the results compared to smaller clinical trials.

In the meta-analysis we chose to use the random-effects model over the fixed-effects model. We chose this since we could not be certain that all studies had evaluated and measured the outcomes totally identical. The random-effects model will assign

more power to the smaller studies than the fixed-effects model will due to the incorporated heterogeneity in the analysis. This can pose a challenge when the smaller studies present different results than larger studies (due to publication bias), since the random-effects model will exaggerate the often-positive effect of the smaller studies, and thereby be subject to a higher degree of bias. In the evaluation of bias of the non-randomized studies we chose to use the Newcastle-Ottawa scale (60). As opposed to the bias evaluation of randomized trials in meta-analyses, the bias evaluation of non-randomized studies in meta-analyses is to a larger degree characterized by uncertainty due to lack of consensus. More than 86 different scales, scores and checklists have been developed to evaluate the risk of bias in non-randomized studies each with different strengths and limitations (143). The Cochrane collaboration recommends the use of either the Newcastle-Ottawa scale (60) or the Downs and Black checklist (144) in evaluating the risk of bias in non-randomized studies (61). The reason why we chose to use the Newcastle-Ottawa scale was because it is divided into two separate scales according to study design (i.e. case-control and cohort studies). Even though the Newcastle-Ottawa scale has been increasingly used in published meta-analyses of non-randomized studies and is considered the suggested scale of choice, several critics have pointed out difficulties in inter-rater reliability when using the scale (78,145).

Several perspectives can be drawn from the included studies in this thesis. First of all, it has been concretized that patient-related risk factors are important when evaluating the risk of recurrence after inguinal hernia surgery. It is not only technical factors such as type of repair, type of mesh, type of fixation, and type of anesthesia that influence the risk of recurrence. The non-technical patient-related risk factors must be seen as supplementary to the technical factors in order to properly evaluate how and when to treat patients for their groin hernias and who are at specific risk of returning with a recurrence. Non-technical risk factors for recurrence are universal and much less prone to variation from case to case as the technical risk factors can be. The non-technical risk factors are not subject to manipulation, learning curves, or personal errors as the technical factors can be. The technical factors greatly rely on the controllable surroundings and the technique and experience of the operating surgeon. The studies included in this thesis indisputably show, that non-technical risk factors for recurrence must be taken into consideration if trying to reduce the risk of recurrence after inguinal hernia surgery. We found that the type of hernia had great influence on the risk of recurrence and the type of recurrence, and furthermore that the optimal type of repair differed between genders and the type of hernias (2,3). A clinical perspective of this knowledge could be to implement preoperative ultrasonography of groin hernias in the future. Ultrasonography has been shown to have a very high sensitivity and specificity (96 % and 99 %, respectively) in classifying groin hernias after a learning curve of 20 hernias for a radiologist (146). By knowing the subgroup of patients with particular risk (i.e. by the hernia type in combination with other patient-related risk factors) it could be possible to stratify patients to different preoperative information, to different surgical techniques, and together with the operative findings provide stratified postoperative follow-up.

Countries in the Western world are predicted to experience tendencies towards increasing age among its populations and as a necessary consequence of this the percentage of elderly inhabitants will constitute a larger share of the population in the future (6). As documented (1), it is primarily elderly people who undergo groin hernia repair and with constantly aging populations, groin

hernia repair will likely pose an increasing problem in the future (147). The reason to why inguinal hernias recur is most likely multifactorial and lies in the span of technical and non-technical patient-related risk factors. The risk factors presented in this thesis have shown to have major influence on the risk of being reoperated after inguinal hernia reoperation.

## FUTURE STUDIES

The studies included in the thesis have studied the natural history of groin hernias on a nationwide basis; have identified the epidemiologic distribution of groin hernias on a nationwide basis; and assessed the non-technical patient-related risk factors associated with recurrence. However, the aim of this kind of research will always be to create evidence that ultimately can be used to reduce morbidity and mortality as well as increase the quality of life for persons affected by groin hernias. The fact that we have shown strong associations between risk factors and recurrence as outcome does not make us capable to estimate causal relationships (148). Future studies should therefore explore:

- why a difference in reoperation rates actually exist between the different inguinal hernia subtypes and if a systemic component exists in one of the subtypes that can explain these differences
- why indirect inguinal hernias in males operated by laparoscopy have higher reoperation rates than indirect inguinal hernias operated by Lichtenstein's technique
- if implementing preoperative ultrasonography of groin hernias can lead to a risk stratification of a subgroup of patients that need special preventive attention
- why inguinal hernias predominantly are common in males and femoral hernias predominantly are common in females
- the genetic and inheritable aspects of groin hernias

## SUMMARY

### Background

Recurrence after inguinal hernia surgery is a considerable clinical problem, and several risk factors of recurrence such as surgical technique, re-recurrence, and family history have been identified. Non-technical patient related factors that influence the risk of recurrence after inguinal hernia surgery are sparsely studied. The purpose of the studies included in this Ph.D. thesis, was to describe the epidemiologic characteristics of inguinal hernia occurrence and recurrence, as well as investigating the patient related risk factors leading to recurrence after inguinal hernia surgery. Four studies were included in this thesis.

### Methods and results

#### Study 1

The study was a nationwide register-based study combining the Civil Registration System and the Danish National Hospital Register during a five-year period. We included a total of 46,717 persons operated for a groin hernia from the population of 5,639,885 people (2,799,105 males, 2,008,780 females). We found that 97 % of all groin hernia repairs were inguinal hernias and 3 % femoral hernias. Data showed that inguinal hernia surgery peaked during childhood and old age, whereas femoral hernia surgery increased throughout life.

#### Study 2

Using data from the Danish Hernia Database (DHDB), we included all male patients operated for elective primary inguinal hernia during a 15-year period ( $n=85,314$ ). The overall inguinal hernia reoperation rate was 3.8%, and subdivided into indirect inguinal hernias and direct inguinal hernias, the reoperation rates were 2.7 % and 5.2 %, respectively ( $p<0.001$ , Chi-square). In the multivariate Cox proportional hazards analysis of factors predicting reoperation, we found that a direct inguinal hernia at primary operation was a substantial risk factor for recurrence with a Hazard ratio of 1.90 (CI 95% 1.77 – 2.04) compared with an indirect inguinal hernia at primary operation ( $p<0.001$ ). We found that there was a significant relationship between the type of hernia at the primary operation and reoperation, when controlling for the effect of the operation method,  $r=0.45$  ( $p<0.001$ ). This corresponded to odds ratios (OR) of 7.1 (CI 95% 6.0-8.4) of being reoperated for a direct inguinal hernia if the hernia at the primary operation was a direct inguinal hernia, and an OR of 3.0 (CI 95% 2.7-3.3) of being reoperated for an indirect inguinal hernia if the primary operation was for an indirect inguinal hernia. As subsequent findings, we saw that the frequency of laparoscopic hernia repair increased during the study period and that the laparoscopic repair of indirect inguinal hernias recurred more often than indirect inguinal hernias operated by Lichtenstein's technique ( $p<0.001$ ).

#### Study 3

Using data from the DHDB, we included all female patients operated for elective primary inguinal hernia during a 15-year period ( $n=5,893$ ). Of those, a total of 305 operations for recurrences were registered (61 % inguinal recurrences, 38 % femoral recurrences, 1 % no hernial), which corresponded to an overall crude reoperation rate of 5.2 %. A noticeable difference was found in reoperation rates after primary operation for direct inguinal hernias (DIH), indirect inguinal hernias (IIH) and combined IIH+DIH of 11.0 %, 3.0 %, and 0.007 % respectively ( $p<0.001$ , Chi-square). In the multivariate Cox proportional hazards analysis of factors predicting reoperation, we found that a direct inguinal hernia at primary operation was a substantial risk factor for recurrence with a Hazard ratio of 3.1 (CI 95% 2.4 – 3.9) compared with an indirect inguinal hernia at primary operation ( $p<0.001$ ). Laparoscopic operation was found to give a lower risk of recurrence with a Hazard ratio of 0.57 (CI 95% 0.43-0.75) compared with Lichtenstein's technique ( $p<0.001$ ). We found that all femoral recurrences ( $n=116$ ) occurred after Lichtenstein's procedure and none occurred after laparoscopic operation ( $p<0.001$ , Log Rank test).

#### Study 4

This study was a systematic review and meta-analysis of non-technical patient-related risk factors for recurrence after inguinal hernia surgery. From a total of 5,061 potentially relevant records we included 40 studies in the review covering 719,901 procedures in 714,167 patients and of those 14 studies covering 378,824 procedures in 375,620 patients were included into meta-analysis of eight risk factors (gender, age, hernia type, hernia size, re-recurrence, bilaterality, mode of admission and smoking). We found that female gender (RR 1.38, 95 % CI 1.28 – 1.48,  $I^2 = 0$  %), direct inguinal hernias at primary procedure (RR 1.91, 95 % CI 1.62-2.26,  $I^2 = 10$  %), operation for a recurrent inguinal hernia (RR 2.2, 95 % CI 2.0-2.42,  $I^2 = 6$  %), and smoking (OR 2.53, 95 % CI 1.43-4.47,  $I^2 = 0$  %) were risk factors for recurrence after inguinal

hernia surgery. Furthermore, emergency admission; connective tissue composition and degradation; and positive family history were found to have an impact on the risk of recurrence, while post-operative convalescence and age had no impact on the risk of recurrence.

### Conclusion

The studies included in the thesis have studied the natural history of groin hernias on a nationwide basis; have identified the epidemiologic distribution of groin hernias and the non-technical risk factors associated with recurrence. Data showed that non-technical patient-related risk factors have great impact on the risk of recurrence after inguinal hernia surgery. The reason to why inguinal hernias recur is most likely multifactorial and lies in the span of technical and non-technical patient-related risk factors and it is possible that the different groin hernia subtypes have different pathophysiology. This knowledge should be implemented into clinical practice in order to reduce the risk of recurrence and in future research design examining recurrence after inguinal hernia surgery as outcome.

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