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REVIEW

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Open mesh versus non-mesh repair of groin hernia meta-analysis of randomized trials leased on individual patient data

The EU Hernia Trialists Collaboration

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Abstract *Background*. The EU Hernia Trialists Collaboration was established to provide reliable evaluation of newer methods of groin hernia repair. It involved 70 investigators in 20 countries.
Materials and methods. Twenty eligible trials (5016 participants) of open mesh vs. non-mesh groin hernia repair were identified. Meta-analysis was performed using raw individual patient data where possible.
Results. Fewer hernia recurrences were reported after mesh repair. There were no clear differences between mesh and non-mesh groups in complications. Overall, those in the mesh groups had a shorter hospital stay, quicker return to usual activities and less frequent persisting pain, but individual trial results varied.
Conclusions. The review provides strong evidence that open mesh repair is associated with a reduction in the risk of recurrence of between 50% and 75%. There is also some evidence of quicker recovery and of lower rates of persisting pain following open mesh repair.

Keywords Inguinal hernia · Individual patient data meta-analysis · Systematic review · Randomised controlled trial · Synthetic mesh

Introduction

The EU Hernia Trialists Collaboration is a group of 70 surgical trialists from 20 countries who had participated in randomised controlled trials of open tension-free or laparoscopic groin hernia repair [7]. The aim was to synthesise data from comparable trials to provide clearer evidence on the advantages and disadvantages of newer methods of groin hernia repair. Estimates of effect would be statistically more precise because of the larger numbers analysed, and consistency across trials would increase generalisability. However, systematic reviews of the data in published reports [8, 9] proved to be limited by the incompleteness of the data available. Information about the pre-chosen outcome measures was often not available, and where it was, it was commonly not in a form suitable for meta-analysis. In the study reported here, raw datasets (individual patient data, IPD) were requested for each of the participating trials. These were then reanalysed centrally and used to derive much more complete and hence reliable meta-analyses. The results for the comparison of laparoscopic vs. open repair, also based on IPD, have been published previously [10], and we now present the results of the open mesh vs. non-mesh comparison. These are short versions of the full report of the work which is being published concurrently in the Cochrane Library [15, 23].

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Material and methods

Our methods followed those of the Cochrane Collaboration [4]. All randomised and quasi-randomised controlled trials of mesh techniques vs. non-mesh techniques for open groin hernia repair were eligible for inclusion. If the method of randomisation was not specified, the trial was still included. Trials were included irrespective of the language in which they were reported. The trials included patients with a clinical diagnosis of groin hernia for whom surgical management was judged appropriate; in addition to primary inguinal hernia, this included patients with femoral, recurrent and bilateral hernias.

Collaboration members met face to face at three meetings, with workshops to develop and agree the protocol. The pre-stated outcomes were: duration of operation, surgical complications, length of hospital stay, time to return to usual activities, pain and numbness persisting longer than 3 months, and hernia recurrence. The work was coordinated by a statistical secretariat.

Selection of studies

The electronic bibliographic databases Medline and the Cochrane Central Controlled Trials Registry were searched first. In Medline the first two stages of the standard Cochrane search strategy described by Dickersin et al. [6] were used with the appropriate

specific search terms for inguinal hernia repair. Further trials were identified from the reference lists of reports of known trials, relevant websites, and by word of mouth through the Collaboration. Trials were identified up to June 2000, and data collection was closed in July 2000.

Data collection and analysis

Raw, IPD were sought by the Secretariat for all patients randomised in all eligible published and unpublished randomised controlled trials and follow-up beyond that previously published was requested. These datasets were then recoded by the Secretariat into a standard format. Summary statistics were generated for each outcome. The IPD were thoroughly checked for internal consistency and consistency with any published reports. Routine checks for randomisation integrity were also made including checks for balance in numbers randomised to each arm and in baseline categories. Graphs were also produced to examine the pattern of randomisation to each group by date. These checks were used for guidance only, and no studies were excluded as a result. Any apparent discrepancies and queries were resolved by discussion with the responsible trialists who also verified the final version of the analyses for each trial. All analyses were based on the original allocation regardless of the actual method of repair performed ('intention to treat'). If patients had been excluded because they did not receive the allocated procedure, details were sought and included where possible.

All studies were assessed for methodological quality and outcome data abstracted. Two reviewers performed this independently. Where a difference of opinion existed, another member of the review team acted as arbiter. Some denominators were unclear for dichotomous outcomes and were assumed to be the numbers randomised. For a small number of trials standard deviations were estimated using data from other trials in the review.

Where IPD were not available, aggregated data were used; the trialist was asked to verify information abstracted from their publication and supplement this where possible. When neither IPD nor additional aggregate data were available, published data taken from the trial reports were used.

For most dichotomous outcomes data were combined using Peto's odds ratio (OR) method and data for continuous outcomes combined using the weighted mean difference. For time to return to usual activities the results from IPD were combined using hazard ratios (HR). The primary results are reported using a fixed-effect model. The χ^2 test was used to test for heterogeneity across studies, and where significant heterogeneity was found possible reasons were explored.

Some non-mesh arms included a mixture of Shouldice and other non-mesh repairs. Where possible, we used the IPD to split a trial into two groups of centres which mainly used the different types of repair, and included the resulting two strata of the trial separately in our meta-analyses. Where this was not possible, the trial was included according to the most common type of repair used.

Duration of operation was defined as time from first incision to final stitch. Other definitions, such as time in theatre, were used if this was not available. 'Opposite' method was defined as mesh repair actually initiated when randomised to non-mesh, or vice versa. Haematoma included wound or scrotal haematoma or ecchymosis but not bruising; seroma included hydrocoele. Wound/superficial infection comprised wound-related infections only, and pus from wound, fistula and sinus formation were all included within this definition. Serious complications included potentially life-threatening visceral and vascular injuries, and mesh or deep infections. If length of postoperative stay was not available, time from admission to discharge was used instead. 'Usual activities' were defined as normal social activities but if this was not available work was used instead. Persisting pain was defined as groin, thigh or testicular pain (including slight) 1 year after the operation or at the closest time point to 1 year, provided it was more than 3 months post-surgery. Persisting numbness was defined in the same way and included paraesthesia, dysaesthesia and discomfort. Reports of hernia recurrence were included regardless of whether it was stated that the recurrence was clinically confirmed.

Results are presented such that OR (or HR) values less than unity, and negative weighted mean differences indicate a favouring of mesh repair. Trials are grouped according to whether flat mesh, plug and mesh or preperitoneal mesh was used, and in addition flat mesh trials have been grouped according to whether the non-mesh method was Shouldice. If a trial contributes to more than one comparison it only contributes once to the overall effect estimate.

Results

Twenty studies comprising a total of 5016 randomised participants were identified that met the eligibility criteria; this included two unpublished studies (Girão, unpublished; Nordin, unpublished) identified through the Collaboration. Seventeen used flat mesh, two plug and mesh [19, 26] and one preperitoneal mesh [12]. A variety of different types of non-mesh repair were used: Shouldice in eight trials [1, 3, 5, 13, 14, 16, 22, 26] and those of Girão (unpublished) and Nordin (unpublished) and a mixture of techniques in five [2, 11, 12, 24, 25]. The trials ranged in size from 80 to 672 randomised participants. Participants received general, spinal or local anaesthesia determined by the trial protocol or surgeon's choice. The characteristics of the 20 trials are described in detail elsewhere [23].

Individual patient data were received for 11 studies comprising 3347 participants with additional aggregated data for a further four (795 participants). Only published data were available for the remaining five studies (874 participants): three reported as full publications and two as conference abstracts which were identified too late to allow time to approach the trialists.

Only five trials reported that a method of allocation concealment (all sealed envelopes) was used. Of the remaining 15 trials three reported the use of random number tables or computer randomisation and one reported randomisation stratified by surgeon. Two trials ([16], Girão, unpublished) are known to have used an inadequate method of concealment (the coin toss method). The method of allocation concealment is not known for the remaining trials.

There was marked heterogeneity in respect to duration of operation (Fig. 1). To an important extent this reflected differences in the type of non-mesh procedure performed. Open flat mesh methods took an average 6–9 min fewer to perform than Shouldice procedures was but 1–4 min longer than other open non-mesh methods.

Only one study [1] reported that patients had not received the randomised operation. Thirteen patients in three studies were known to have been converted to the opposite type of repair: seven originally allocated mesh and six originally allocated non-mesh.

There were no clear differences in reports of haematomas (overall Peto OR 0.93, 95% CI 0.68–1.26, $P = 0.6$); seromas (overall Peto OR 1.52, 95% CI 0.92–2.52, $P = 0.1$); and wound/superficial infections

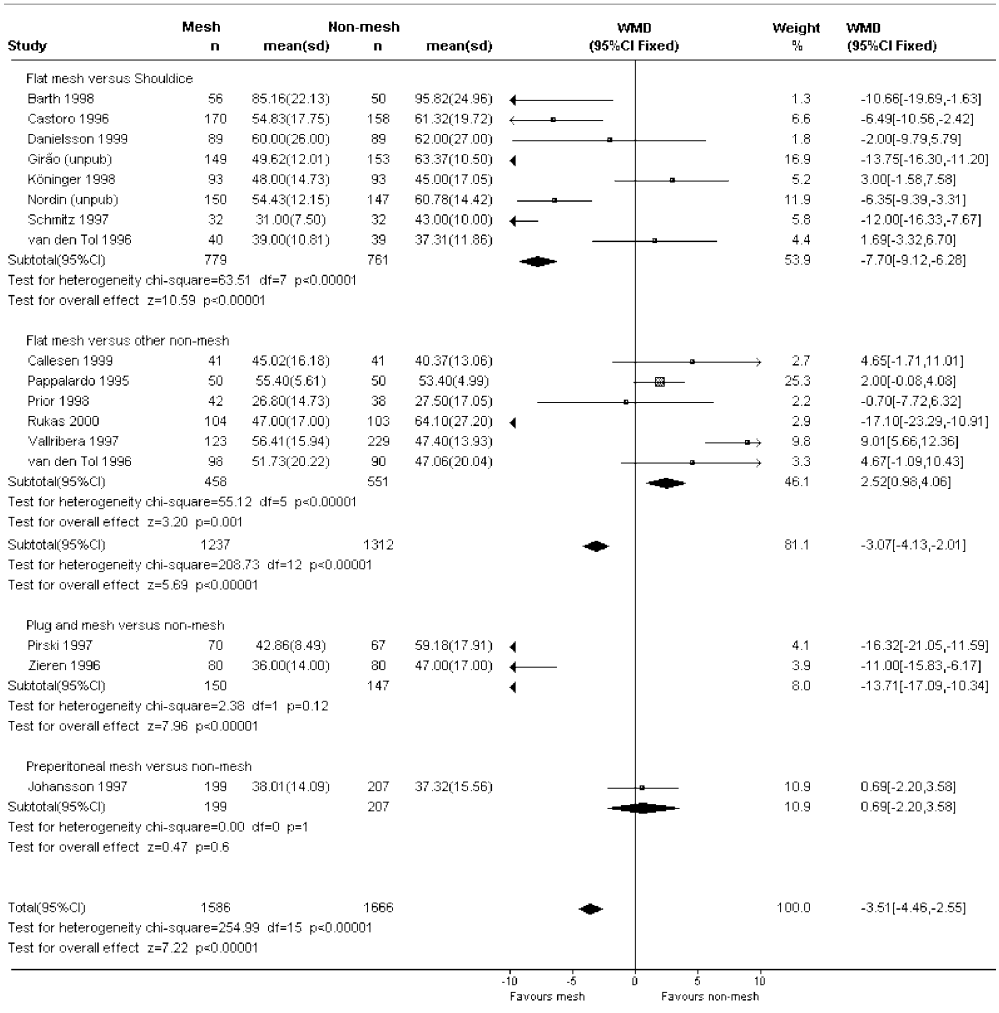

Fig. 1. Duration of operation (minutes). *Solid squares* Individual weighted mean differences; *horizontal lines* 95% confidence intervals (*CI*); *diamonds* pooled weighted mean differences; *sd* standard deviation; *df* degrees of freedom; *WMD* weighted mean difference

(overall Peto OR 1.24, 95% CI 0.84–1.84, $P = 0.3$), and this was found irrespective of the types of operation being compared (data available elsewhere [23]).

Serious operative complications were rare. After allocation to open mesh repair there was one bowel perforation (Nordin, unpublished), a reoperation for haematoma [3] and a reoperation for bleeding [12]. Following allocation to non-mesh repair there was one visceral injury (type not known) [18], one vascular injury (type not known) [18] and one deep infection [12].

Overall, length of postoperative hospital stay was shorter following mesh repair by between 0.22 and 0.35 days (data available elsewhere [23]). There was considerable heterogeneity, which was not explained by the method of non-mesh repair. The individual trials fell into two groups. One group (11 trials) showed no difference, whereas the other group (6 trials) showed clearly shorter stays after mesh repair. This pattern is likely to reflect the discharge policies used by the hospitals during the trials.

Overall, return to usual activities or work was shorter following mesh repair (overall HR 0.81, 95% CI 0.73–0.91, $P < 0.001$; Fig. 2). However, again, there was heterogeneity. To an extent this was explained by one trial [18]. After removal of these data the result was not statistically significant (HR 0.89, 95% CI 0.80–1.00, $P = 0.06$).

The available data suggest that persisting pain was less frequent after mesh repair (overall Peto OR 0.68, 95% CI, 0.47–0.98, $P = 0.04$; Fig. 3). However, this result was dependent on one trial [13] which had high rates of pain, and data were available for only nine of the 20 eligible studies and therefore should be interpreted very cautiously. As there was marked heterogeneity a random effects model was also fitted for these data (OR 0.86, 95% CI 0.43–1.73, $P = 0.7$). Persistent numbness was reported in only three trials, and then only infrequently (Peto OR 0.70, 95% CI 0.29–1.72, $P = 0.4$).

Recurrence after mesh repair was consistently less often reported in individual trials (11 vs. 2 trials) and overall was reduced by between 50% and 75% (Peto OR 0.37, 95% CI 0.26–0.51, $P < 0.001$; Fig. 4). This was seen regardless of whether Shouldice or another non-mesh method was used. In the one trial that was inconsistent with the overall pattern [12] a preperitoneal technique was used.

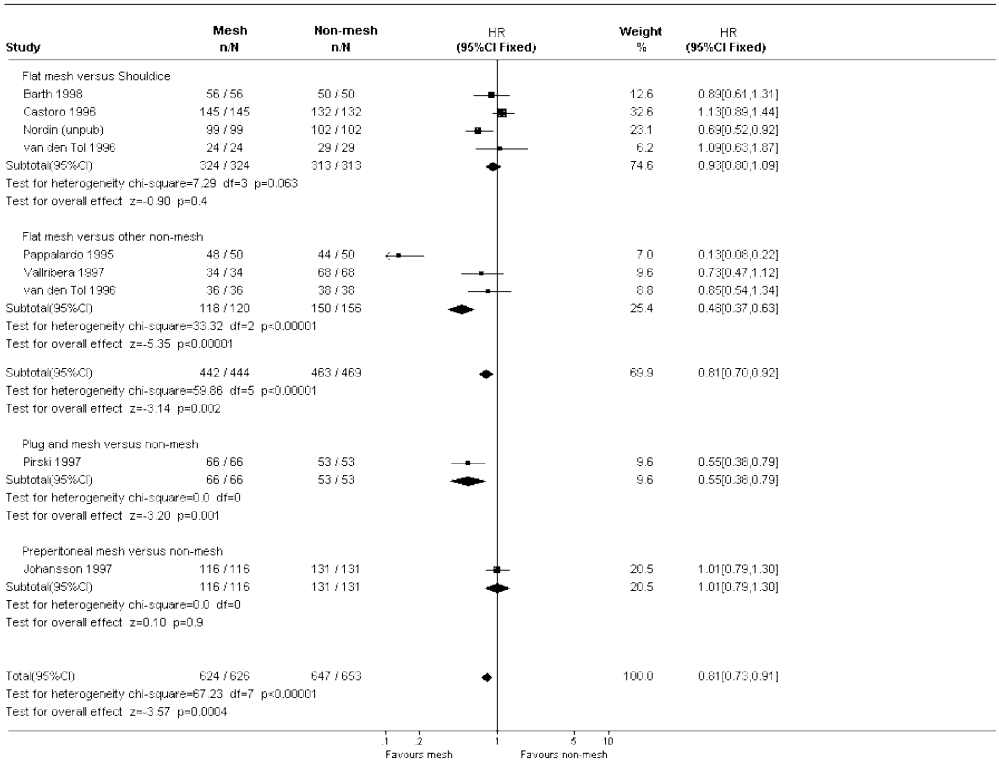

Fig. 2. Return to usual activities. *Solid squares* Individual hazard ratios; *horizontal lines* 95% confidence intervals (*CI*); *diamonds* pooled hazard ratios; *df* degrees of freedom; *HR* hazard ratio

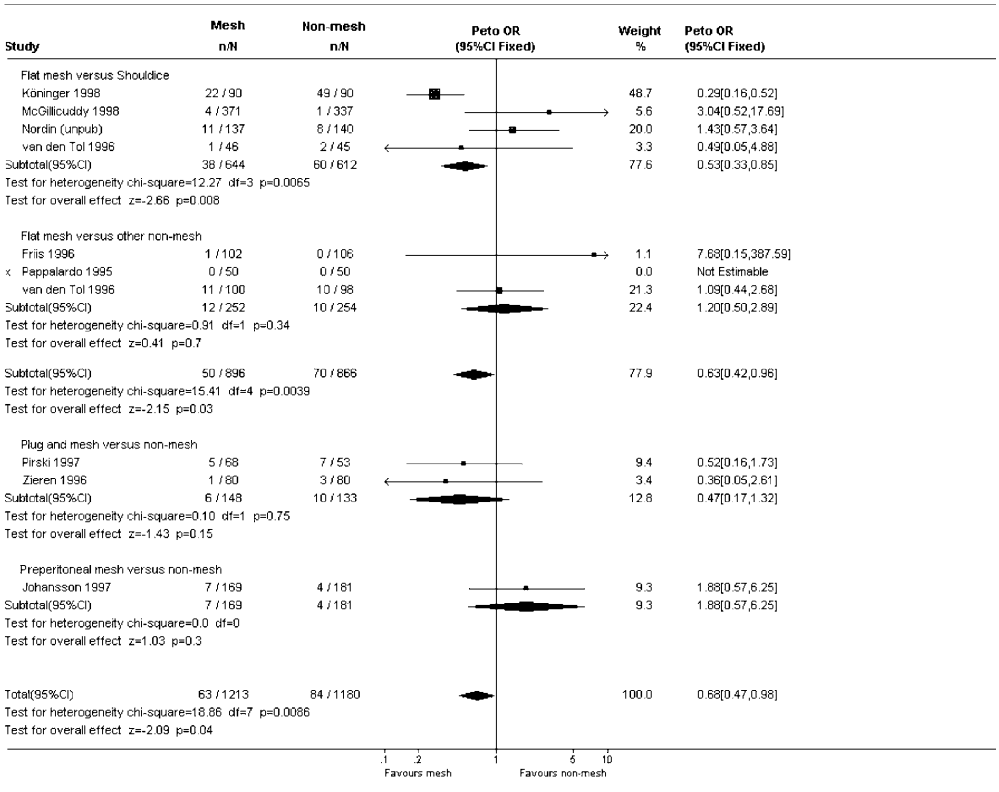

Fig. 3. Persisting pain. *Solid squares* Individual odds ratio; *horizontal lines* 95% confidence intervals (*CI*); *diamonds* pooled odds ratio; *df* degrees of freedom; *OR* odds ratio

Thirty-one participants in the trials are known to have died. There was no evidence of a difference between the mesh and non-mesh groups and no death was related to trial surgery.

Three pre-specified subgroup analyses were performed: patients with recurrent hernias, bilateral hernias and femoral hernias. There were too few data to reliably compare mesh and non-mesh techniques in these specific

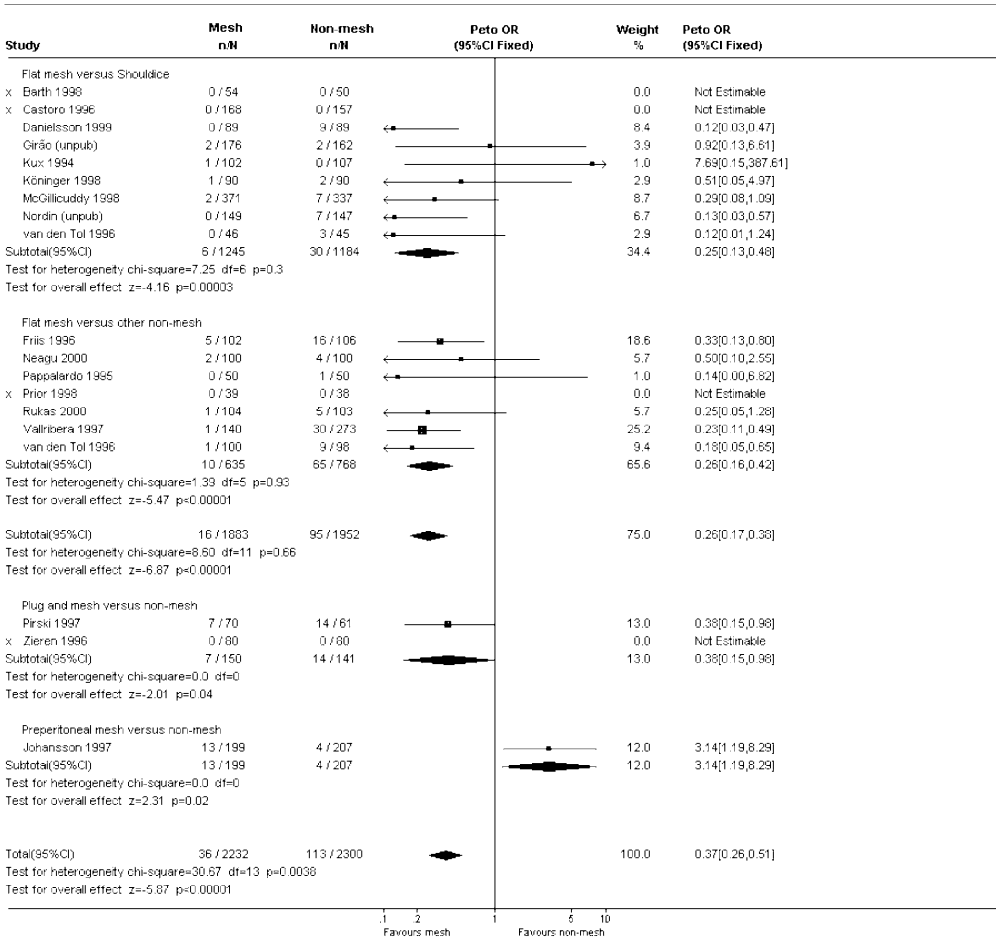

Fig. 4. Hernia recurrence. *Solid squares* Individual odds ratio; *horizontal lines* 95% confidence intervals (*CI*); *diamonds* pooled odds ratio; *df* degrees of freedom; *OR* odds ratio

circumstances (see Cochrane review for details [23]). Data were available only for two trials for recurrent hernias [12, 19], two trials for bilateral hernias [19] (Girão, unpublished) and one trial for femoral hernias [19], and there were no available data for some comparisons.

Discussion

Our results provide strong evidence that the use of mesh in open repair is associated with a substantial reduction in the risk of recurrence of between 50% and 75%. The Shouldice repair is widely regarded as the gold standard non-mesh open method, but the difference was observed regardless of whether the type of non-mesh repair was Shouldice. Although the trials showed some heterogeneity, there is also an indication that mesh repair is associated with faster return to normal activities and with lower rates of persisting pain. No clear differences were observed with respect to operative complications or persisting numbness. Mesh is not available in some countries because of the associated additional costs, but an economic evaluation (not reported here) suggests that these are offset over one to 4 years by the reduced costs of reoperation following recurrence.

This review was conducted through the formal structure of the EU Hernia Trialists Collaboration which ensured as complete identification as possible of relevant trials. Two unpublished trials were identified and included in this review. In addition, individual patient data were received for 11 studies and additional aggregated data for a further four of the 20 eligible. This greatly enhanced the amount of data that could be included in the review compared with the original version based on published data [8] and helped ensure a higher standard of data and randomisation integrity. However, despite maximum effort, published data had to be used for five trials (two of which were reported as conference abstracts shortly before data collection closed), and the usefulness of these was often limited by the way in which the data were reported.

It has been suggested that specific types of repair may be optimal for different types of patients, such as those with recurrent, bilateral or femoral hernias. However, although we were able to collect the raw data for many trials, there were still insufficient data to explore the differential effects of mesh or non-mesh repair for these subgroups of patients. We also found insufficient evidence to reliably address different types of open mesh repair, particularly flat mesh and plug and mesh repair.

To our knowledge, this is the first time that trialists in general surgery have collaborated in this way by contributing their trial data for the purposes of a systematic review. We have demonstrated that, although costly, the collection of IPD can greatly enhance the data available for a systematic review compared with using published data alone.

An important finding was less persisting pain after mesh repair. However, this was based on a minority of trials and we use a broad 'inclusive' definition. Further research could clarify whether there really is less persisting pain after mesh repair, and, if so, whether this applies to severe pain. Also, the site of any persisting pain may depend on the type of repair and this too merits further research.

There are currently too few data to test for differential effects of mesh vs. non-mesh in the specific subgroups of recurrent hernia, bilateral hernia and femoral hernia. Ideally, further trials should be conducted in these specific clinical groupings.

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