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Meta-analysis of health-related quality of life after minimally invasive versus open oesophagectomy for oesophageal cancer

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Title: Health-related quality of life after minimally invasive versus open oesophagectomy for oesophageal cancer - a systematic review and a meta-analysis

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Abstract

Background: The aim of this systematic review and meta-analysis was to compare health-related quality of life (HRQOL) outcomes between minimally invasive and open oesophagectomy for cancer at different postoperative time points

Methods: A search of PubMed (MEDLINE), Web of Science, EMBASE, Scopus, CINAHL and Cochrane Library was performed, yielding 2853 titles. Nine studies comparing patients who underwent minimally invasive surgery (n=1161) with those who underwent open surgery (n=903) were included in the systematic review based on eligibility criteria. A random-effects meta-analysis was conducted based on eight studies that measured HRQOL scores using the EORTC QLQ-C30 and QLQ-OES18 questionnaires. Mean score differences (MSD) >10 were considered clinically relevant. Pooled effects of MSD with 95% confidence intervals (CI) were estimated to assess statistical significance.

Results: Patients who underwent minimally invasive surgery had on average better scores for global quality of life (MSD 11.6, 95% CI 3.8 to 19.4), physical function (MSD 11.9, 95% CI 3.9 to 19.8), fatigue (MSD -13.2, 95% CI -17.6 to -8.8), and pain (MSD -15.9, 95% CI -20.5 to -11.2) than those who underwent open surgery at 3 months after surgery. At 6 and 12 months after surgery, no significant differences remained.

Conclusion: This meta-analysis indicates **better average global** quality of life, physical function, fatigue and pain 3 months following minimally invasive surgery compared to open surgery. No such differences remain at longer follow-up of 6 and 12 months. This knowledge can guide clinical decision-making and improve patient information.

Introduction

Oesophageal cancer is the 9th most common cancer and the 6th most common cause of cancer death worldwide.¹ The mainstay curative option for most patients with locally advanced cancer is oesophagectomy, often preceded by neoadjuvant therapy.² Surgical resection is associated with a high rate of post-operative morbidity, and health-related quality of life (HRQOL) can deteriorate substantially following such radical surgery.³ In recent years minimally invasive techniques using a combination of thoracoscopic and/or laparoscopic approaches have been used increasingly, with the primary aims of reducing surgical trauma, minimising complications and improving postoperative recovery.⁴ In addition to a few cohort studies, one randomized clinical trial has indicated that specific components of short-term HRQOL may be improved through utilization of a minimally invasive approach to esophagectomy.⁵ However, great variability exists regarding which HRQOL outcomes have been assessed and the time period after surgery that these were evaluated.^{6, 7} There is presently no conclusive evidence as to whether HRQOL in general is improved following minimally invasive oesophagectomy compared to open surgery, if any specific HRQOL outcomes differ between these approaches and the length of time these persist following surgery.

Therefore, the aim of this systematic review and meta-analysis was to clarify potential differences in postoperative HRQOL outcomes over time after minimally invasive compared to open oesophagectomy for oesophageal cancer.

Methods

This systematic review was conducted according to the PRISMA guidelines.⁸ An a priori established detailed study protocol was followed.

Search strategy

A comprehensive literature search was conducted in September 2016 using a keyword search on PubMed (MEDLINE), Web of Science, EMBASE, Scopus, CINAHL and Cochrane, from the inception of each database. The following search string was used: (mini-invasiv* OR minimally-invasive OR minimally invasive OR vats OR thoraco* OR laparo*) AND (esophag* OR oesophag* OR gastro-oesophag* OR gastroesophag*) AND (neoplas* OR tumo* OR cancer OR carcinoma OR adenocarcinoma) AND (Quality of life OR qol OR hqol OR hrqol).

Study selection

Studies considered for inclusion in the systematic review and meta-analysis had the following characteristics:

- 1) Original studies.
- 2) Written in English.
- 3) Oesophageal cancer or high-grade dysplasia (HGD) were primary indications for oesophagectomy.
- 4) HRQOL data were assessed using any well-validated HRQOL instrument or its derivative.
- 5) HRQOL outcomes were measured both before and after the oesophagectomy.
- 6) Post-operative HRQOL was compared between minimally invasive and open surgical procedures.

The search identified 2853 titles. The titles and abstracts of these studies were evaluated. When the studies seemed to meet the eligibility criteria, or when information was insufficient

to exclude them, the full articles were reviewed. The reference lists of the retrieved articles, PubMed “related articles” and articles dealing with the literature review were scanned for potential additional studies. After the search, one author (J.H.K.) performed the screening of all titles and abstracts. Studies were included according to the eligibility criteria above. After the initial screening, full text articles were obtained. Full-text articles were independently studied by two authors (J.H.K., and P.L.). In the case of discrepancies, the studies were discussed based on the pre-determined eligibility criteria between the authors and resulted in a consensus decision. The workflow is summarized in Figure 1.

Data extraction

All data from eligible studies were independently extracted by two investigators (J.H.K., and S.X.) to maintain the integrity of the data. Gathered information included the name of first author, publication year, study period, design, population characteristics (age and sex), treatment, number of patients in the two surgery groups, HRQOL indicators used and HRQOL outcomes at baseline and different time points after surgery. First authors and corresponding authors in the eligible studies were contacted by email up to three times to obtain unreported data.

Quality assessment

Study quality and bias were assessed separately by two authors (J.H.K. and P.L.) using the Newcastle-Ottawa scale, as all but one of the included studies were cohort studies.⁹ The pre-determined items for assessment of study quality and results were used to rank the studies. Discrepancies between assessors were settled upon discussion. Bias in individual studies was analysed qualitatively.

Definition of exposure and outcome

The study exposure was divided in two categories, namely minimally invasive oesophagectomy and open oesophagectomy. Minimally invasive oesophagectomy included hybrid approaches such as laparoscopic-assisted, hand video-assisted and thoracoscopic-assisted, and totally minimally invasive (both laparoscopic and thoracoscopic) procedures. Open procedures included Ivor-Lewis- and left transthoracic thoraco-abdominal oesophagectomy (with intra-thoracic anastomosis), three-incision oesophagectomy (with neck anastomosis), and transhiatal oesophagectomy (with neck anastomosis).

Outcome of interest was HRQOL, a multidimensional measure consisting of physical health, psychological health, functional status, social relationships, and personal beliefs.¹⁰ HRQOL can be classified as generic or disease-specific and measured using a variety of scales and indicators. The HRQOL questionnaires that were used in the included studies were the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 v3.0 core questionnaire (EORTC QLQ-C30) measuring cancer-related functions and symptoms,¹¹ EORTC oesophageal cancer-specific HRQOL module (EORTC QLQ-OES18) assessing disease related symptoms and items,¹² short-form health survey (SF-36) measuring general health,¹³ the Multi-Dimensional Fatigue Inventory (MFI-20) measuring different aspects of fatigue,¹⁴ a modified Katz Scale and a modified Lawton and Brody Scale measuring daily activities.¹⁵ The HRQOL questionnaires used in the studies were checked for validity in the native languages of the countries of origin specified in Table 1.

Statistical analysis

The statistical analyses were performed using RevMan version 5.3 (The Cochrane Collaboration, Oxford, UK) and STATA version 13.0 (StataCorp LP), according to the Cochrane guidelines for systematic reviews.⁹ Number of the patients in each treatment group

was collected as reported in the individual studies. Standard deviations were calculated based on the standard error of the mean value and patient number at each time point for each of the two surgery groups. Missing data on standard deviations were imputed using the largest reported standard deviation for the outcome with the given surgical operation at a given time point.^{9, 16} This approach was used to obtain the most conservative effect estimate. Data available only in graphical format were extracted using the WebPlotDigitizer tool (<http://arohatgi.info/WebPlotDigitizer>). In one included study,¹⁷ two open oesophagectomy procedures were combined as suggested in the Cochrane Handbook.⁹ To evaluate potential bias due to imputation of standard deviations for two of the included studies, we performed a sensitivity analysis including only the studies that did not require any data to be imputed.

Continuous variables were analysed using inverse variance according to the DerSimonian-Laird method.¹⁸ To obtain estimates of the average treatment effects, a random effects model was used to estimate mean differences for continuous data across the studies.¹⁹ Mean score differences (MSD) and pooled effects with 95% confidence intervals (CI) were depicted on forest plots. Based on previous literature, the mean differences were considered clinically significant only if the pooled differences were at least 10 points, which correspond to at least a “moderate” change or difference for the patients.^{20, 21} Statistical heterogeneity of the studies was assessed in terms of the I^2 statistic.²² An I^2 statistic <25% indicated a minor inconsistency, and an I^2 statistic >50% indicated a major inconsistency. As the random-effects meta-analysis calculates the average effect of a given treatment, 95% prediction intervals were calculated for each outcome at a given time point to estimate the range of true difference between the treatments in 95% of the population.^{19, 23} As the number of included studies was small, meta-regression could not be reliably performed.²⁴ Thus, a sensitivity analysis was undertaken by removing one study at a time in the meta-analysis to estimate the influence of each study on the pooled estimate of HRQOL scores. Potential publication bias and small-

study effects of the clinically relevant HRQOL outcomes were analysed by visually inspecting the funnel plots instead of statistical testing, given the small number of included studies.²⁵

Results

Included studies

Among all 2853 titles, 9 articles published from 2010 to 2016 were eligible for qualitative analysis (Figure 1).^{5-7, 15, 17, 26-29} Main features of these studies are summarized in Table 1. In total, the 9 studies included 2164 patients, of whom 1161 (58.3%) underwent minimally invasive surgery and 903 (41.7%) underwent open surgery. The median number of patients per study was 114 (range 56-888). In three studies, only patients with oesophageal squamous cell carcinoma were included,^{17, 28, 29} while one study included only patients with adenocarcinoma.²⁶ Five studies also included patients with cancer of the gastroesophageal junction,^{5-7, 15, 27} and **two studies** included patients with high-grade dysplasia.^{7, 15} The presence of medical comorbidities was not described in two of the studies,^{15, 27} whereas fitness evaluations with American Society of Anesthesiologists grades (or ASA grades) were available in four studies.^{5, 6, 26, 29} In the 7 studies that described the use of neoadjuvant therapy, 595 (32.4%) of the 1836 patients received such treatment.^{5, 6, 15, 17, 26, 27, 29} The number of patients receiving postoperative chemo- or chemoradiotherapy was described in only one of the 9 studies.²⁶

The main open surgical procedure was the right-sided transthoracic (Ivor-Lewis) oesophagectomy. Less frequent procedures included McKeown modification in an undefined number of patients, as well as left thoracoabdominal and left transthoracic oesophagectomy. No patients undergoing transhiatal resections were included in the studies. Thus, all patients in the open surgery group underwent thoracotomy. There was variability in the anastomotic technique and location. Of patients with minimally invasive surgery, at least 249 underwent totally minimally invasive oesophagectomy in five studies.^{5, 7, 15, 17, 26} Five studies had a hybrid approach or included both totally minimally invasive and hybrid minimally invasive

oesophagectomy in the treatment group (912 patients).^{6, 15, 27-29} One of the studies included a comparison between laparoscopy-thoracoscopy approach and hybrid minimally invasive procedures including laparotomy or thoracotomy.¹⁵ One study utilized hand video-assisted thoracoscopic surgery as the minimally invasive procedure.²⁸ Taken together, all studies included a minimally invasive group of patients who underwent thoracoscopy and an open oesophagectomy group of who underwent thoracotomy. Details on patients and surgery are further described in Tables 2 and 3.

The HRQOL outcomes were measured using both the EORTC QLQ-C30 and the QLQ-OES18 questionnaires in eight studies.^{5-7, 17, 26-29} In one study, MFI-20 and activities of daily living questionnaires suggested decreased fatigue and increased proportion of independent patients after minimally invasive surgery compared to open surgery at 3 and 6 months.¹⁵ All studies using the EORTC questionnaires measured HRQOL at baseline and postoperatively. One of the studies reported one-week outcomes, three studies reported two-week outcomes, four studies reported four-week outcomes, and two studies reported six-week outcomes. Seven of the studies measured HRQOL outcomes at 3-months and six at 6-months after surgery. Four studies measured 12-month HRQOL outcomes and two studies also reported the 24-month outcomes. Reporting on HRQOL outcomes was generally selective; only three articles reported all or almost all of the numerical values for the EORTC QLQ-C30 and QLQ-OES18 questionnaire outcomes. Two studies did not present any numerical values, but instead provided graphs. Only one study used evidence-based cut-off values for interpreting the differences in the HRQOL scores.^{6, 20, 21}

General cancer-related symptoms (EORTC QLQ-C30)

One study measuring fatigue with MFI-20 scale was excluded from the quantitative analysis.¹⁵ The study did not report general fatigue and the subscales were not compatible with fatigue scale in the EORTC questionnaire. The meta-analysis was conducted on 4-6 week and 3-, 6- and 12-month extracted outcome data on global quality of life, physical function, fatigue, and pain from the 8 included studies. Due to the small number of studies reporting outcomes at time points less than 6 weeks postoperatively, outcomes at 4-6 weeks from 5 studies were combined and analysed. Clinical heterogeneity was found between the study populations, as there were differences between the sub-location and histology of the cancers, as well as the study design. The I^2 statistic indicated high statistical heterogeneity (>50%) for all of the analyses, except the global quality of life at 4-6 weeks ($I^2=25\%$) and 12 months ($I^2=9\%$), fatigue at 12 months ($I^2=0\%$) and pain at 4-6 weeks ($I^2=25\%$). However, the baseline values for the studied outcomes in each study were similar in the treatment groups, with no MSD greater than 5 points between surgery groups.

The meta-analyses of these key HRQOL outcomes showed that minimally invasive surgery was followed by better outcomes at 4-6 weeks and 3 months compared to open surgery. The MSDs at 4-6 weeks were 16.1, 95% CI 13.9 to 18.3 for global quality of life, 26.9, 95% CI 19.0 to 34.9 for physical function, -18.8, 95% CI -29.3 to -8.3 for fatigue and -29.0, 95% CI -31.6 to -26.5 for pain. The 3 month outcomes were also better after minimally invasive oesophagectomy for global quality of life (MSD 11.6, 95% CI 3.8 to 19.4), physical function (MSD 11.9, 95% CI 3.9 to 19.8), fatigue (MSD -13.2, 95% CI -17.6 to -8.8), and pain (MSD -15.9, 95% CI -20.5 to -11.2). After 3 months there were no clinically significant MSDs in HRQOL outcomes, except for physical function at 6 months in favor of minimally invasive surgery (MSD 11.8, 95% CI -0.4 to 24.0), but this difference was not statistically significant. The forest plots and pooled estimates for the four outcomes are shown at 4-6 weeks

(Supplementary figure 1), 3 months (Figure 2), 6 months (Supplementary figure 2) and 12 months (Supplementary figure 3). Figure 3 shows the pooled differences of these key outcomes at different time points with 95 CIs. Majority of the patients should experience better global HRQOL and less pain at 4-6 weeks and less fatigue and pain at 3 months after surgery, as reflected by the 95% prediction intervals (Suppl. Figure 4).

The sensitivity analysis of the pooled results excluding the studies using some imputed data showed that the observed pooled clinically significant differences at 3 months remained. The sensitivity analysis omitting one study at a time showed that the omission of one of the studies²⁹ made the 3-month difference of surgical method on global quality of life and physical function clinically less relevant, but the difference remained statistically significant (MSD 8.5, 95% CI 5.6 to 11.4 for global HRQOL and MSD 9.0, 95% CI 4.7 to 13.4 for physical function, at 3 months). Sensitivity analysis was also conducted excluding the studies with hybrid minimally invasive operations. Based on pooled results from two to four studies at each time point, totally minimally invasive surgery had clinically (MSD >10 points) and statistically significant superior outcomes compared to open surgery until 3 months, but not at 6 months, similarly to the main analysis. At 12 months, the difference in global HRQOL was not clinically significant. Other key outcomes at 12 months could not be analysed as data was available from only one study.

Two studies showed decreased dyspnoea symptoms at 4-6 weeks after surgery in favour of minimally invasive esophagectomy.^{27, 29} There were no differences in other function scales (role, emotional, cognitive, or social) or symptom scales and items (nausea and vomiting, insomnia, appetite loss, constipation, diarrhoea, or financial problems) between the groups.

However, the lack of reporting and obtaining the numerical values for these outcomes prevented formal meta-analysis of these outcomes.

Oesophageal cancer-related symptoms (QLQ-OES18)

There were no clinically relevant differences between open and minimally invasive oesophagectomy for most of the QLQ-OES18 outcomes at any time points in any of the studies. Six of the eight studies did not report the numerical data for the outcomes for one or more items. Thus, unbiased meta-analysis of these outcomes could not be performed. One of the studies⁷ reported statistically significant, but not clinically relevant, less oesophageal pain at 3 months, and two studies reported clinically relevant less oesophageal pain at 6 weeks⁵ and 12 months^{5, 6} after minimally invasive surgery compared to open surgery. Also, two studies^{5, 7} reported clinically relevant fewer speech problems at 6-12 weeks postoperatively after minimally invasive surgery compared to open oesophagectomy.

Discussion

The results indicate that minimally invasive surgery is on average followed by better postoperative outcomes regarding global quality of life, physical function, fatigue, and pain up to 3 months after surgery, but these differences fail to persist at 6 or 12 months postoperatively.

Methodological advantages of this meta-analysis include the strict inclusion criteria, use of well-validated questionnaires in all of the included studies, and using a cut-off of 10 for MSDs to reduce bias from multiple testing.^{11, 12, 20, 21} The affected components between the surgical approaches had the same direction of effect at 4-6 weeks and 3 months postoperatively in all studies, suggesting actual effect of the treatment. Additionally, sensitivity analyses by removing any single study, all studies with extracted data or all studies that had hybrid minimally invasive operations from the analysis did not have major effect on the conclusions. Biases in the individual studies might affect the observed pooled effect size. Visual inspection of the funnel plots revealed no evidence of major small-study effects or publication bias. The effect estimates for clinically significant outcomes in the largest study in the meta-analysis were larger than the average effect estimate.²⁹ Thus, no adjustment using the trim and fill method could be reliably done, as suggested earlier.^{30, 31}

The surgical techniques used were variable in both open and minimally invasive groups. All included studies had however a thoracotomy group and a thoracoscopy group. Patients undergoing open surgery had variable procedures, such as Ivor-lewis and left-sided transthoracic oesophagectomy.¹⁷ These operations might have different postoperative recovery profiles. Studies included in the 4-6 weeks outcome analysis were only from Eastern countries, and might not be generalizable for this time point. The results were similar at later

time points with Western studies included. Selective reporting and the inability to obtain the missing data may cause information bias. A weakness was the inability to perform meta-regression and adjust the HRQOL outcomes for confounding, such as neoadjuvant treatment, due to the small number of studies.³² Patients selected for minimally invasive surgery might also be healthier than those selected for open surgery.⁷ Preoperative comorbidities increase complications, as well as poor quality of life outcomes.^{33, 34} Similar in-study preoperative baseline HRQOL values between treatment groups should adjust for some of these differences.^{35, 36} The 95% prediction intervals were calculated to depict the heterogeneity of the studies. It seems that most patients have better global HRQOL and less fatigue at 3 months or less pain up to 3 months after minimally invasive surgery compared to open surgery. Minimally invasive oesophagectomy might reduce complications, which could be the causal link in the improvements in HRQOL up to 3 months following surgery.

This first meta-analysis comparing HRQOL outcomes between minimally invasive and open oesophagectomy identified benefits in four key outcomes following minimally invasive surgery in the short term. No differences remained with longer-term follow up. Most patients are likely to have some benefit from minimally invasive surgery in less pain up to 3 months and less fatigue and better global HRQOL at 3 months after surgery. There are some clinical and research implications that can be drawn from this meta-analysis. Although the 3-month perspective is relevant for patients and healthcare, the lack of differences in HRQOL after this period indicates that open surgery does not need to be abandoned, particularly if the surgeons are more comfortable with open surgery or in patients with contraindications to a minimally invasive approach. The learning curve can decrease the prognosis both in the short- and long term.³⁷ This might be a particular concern for minimally invasive surgery, as shown in esophagectomy,³⁸⁻⁴⁰ as well as other procedures.⁴¹⁻⁴³ Therefore, these results are not enough to

generally recommend minimally invasive oesophagectomy. Patients want information about HRQOL outcomes after cancer surgery, but surgeons rarely inform the patients about such outcomes.⁴⁴ Trauma related to thoracotomy is associated with postoperative pain.^{45, 46} Pain and decreased exertion caused by open surgery may severely influence respiratory function, pulmonary complication rate and postoperative HRQOL.⁴⁷⁻⁴⁹ The present study can help surgeons to inform patients about average effects on HRQOL when making treatment decisions. On-going and future studies and meta-analyses will increase information on the effect of minimally invasive surgery on postoperative HRQOL. Reporting all measured HRQOL outcomes and evaluating the relationship of complications and HRQOL outcomes is important in future studies.

In conclusion, minimally invasive oesophagectomy with thoracoscopy seems to have superior HRQOL outcomes up to 3 months postoperatively compared to open surgery, but no differences remained after this initial postoperative period. These findings cannot be used for any changes in general recommendations on surgical approach, but can help inform the patient about average expected outcomes following oesophageal surgery.

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Figure legends.

Figure 1. Selection of the studies included in the systematic review and meta-analysis.

Figure 2. Results of a meta-analysis of the health-related quality of life (HRQOL) outcomes at 3 months after oesophagectomy for cancer. The mean differences in HRQOL scores are depicted in forest plots, with horizontal lines showing 95% confidence intervals (CI), for global HRQOL (A), physical function (B), fatigue (C) and pain (D). Higher scores in A and B indicate better function and higher scores in C and D indicate worse symptoms. Difference of more than 10 points is considered clinically relevant. IV, inverse variance; MIE, minimally invasive oesophagectomy; OE, open oesophagectomy.

Figure 3. Pooled key health-related quality of life mean score differences (MSD) and 95% confidence intervals (CI) comparing minimally invasive versus open oesophagectomy at different time points. Negative MSDs were converted positive for clarity. Larger MSDs indicate better outcome after minimally invasive compared to open surgery. Dashed horizontal line indicates the threshold for clinical significance of each pooled mean difference.

Supplementary figure 1. Results of a meta-analysis of the health-related quality of life (HRQOL) outcomes at 4-6 weeks after oesophagectomy for cancer. The mean differences in HRQOL scores are depicted in forest plots, with horizontal lines showing 95% confidence intervals (CI), for global HRQOL (A), physical function (B), fatigue (C) and pain (D). Higher scores in A and B indicate better function and higher scores in C and D indicate worse symptoms. Difference of more than 10 points is considered clinically relevant. Number of patients in Maas et al was obtained from Biere et al.⁴ IV, inverse variance; MIE, minimally invasive oesophagectomy; OE, open oesophagectomy

Supplementary figure 2. Results of a meta-analysis of the health-related quality of life (HRQOL) outcomes at 6 months after oesophagectomy for cancer. The mean differences in HRQOL scores are depicted in forest plots, with horizontal lines showing 95% confidence intervals (CI), for global HRQOL (A), physical function (B), fatigue (C) and pain (D). Higher scores in A and B indicate better function and higher scores in C and D indicate worse symptoms. Difference of more than 10 points is considered clinically relevant. IV, inverse variance; MIE, minimally invasive oesophagectomy; OE, open oesophagectomy.

Supplementary figure 3. Results of a meta-analysis of the health-related quality of life (HRQOL) outcomes at 12 months after oesophagectomy for cancer. The mean differences in HRQOL scores are depicted in forest plots, with horizontal lines showing 95% confidence intervals (CI), for global HRQOL (A), physical function (B), fatigue (C) and pain (D). Higher scores in A and B indicate better function and higher scores in C and D indicate worse symptoms. Difference of more than 10 points is considered clinically relevant. IV, inverse variance; MIE, minimally invasive oesophagectomy; OE, open oesophagectomy.

Supplementary figure 4. Pooled key health-related quality of life mean score differences (MSD) and 95% prediction intervals comparing minimally invasive versus open

oesophagectomy for cancer. Negative MSDs were converted positive for clarity. Larger MSDs indicate better outcome after minimally invasive compared to open surgery. Dashed horizontal line indicates the threshold for clinical significance of each pooled mean difference.

Tables

Table 1. Characteristics, quality and HRQOL assessment of the 9 studies included in the systematic review.

Reference	Study interval	Country	Study mode	Study quality	Number of patients	HRQOL questionnaires	Questionnaire compliance	Included time points in months
Barbour, 2016	1998-2011	Australia	Cohort	8	487	QLQ-C30, QLQ-OES18	>95%	3, 6, 12
Hong, 2013	2009-2012	China	Randomized Cohort	8	114	QLQ-C30, QLQ-OES18	93%	1, 3
Maas, 2015	2009-2011	Italy, Netherlands, Spain	RCT	8	115	QLQ-C30, QLQ-OES18, SF-36	82%	1.5, 12
Naftaux, 2011	2005-2010	Belgium	Cohort	7	166	QLQ-C30, QLQ-OES18	86,5%	3, 6, 12
Parameswaran, 2013	2007-2008	U.K.	Cohort	7	86	MFI-20, Brody-lawton, Katz scale	77%	1.5, 3, 6
Shen, 2015	2005-2007	China	Randomized cohort	7	62	QLQ-C30, QLQ-OES18	95%	1, 3, 6
Wang, 2010	2007-2008	China	Cohort	7	56	QLQ-C30, QLQ-OES18	95%	1, 3, 6
Wang, 2015	2004-2013	China	Cohort	7	888	QLQ-C30, QLQ-OES18	100%	1, 3, 6, 12
Zeng, 2012	2010	China	Cohort	8	90	QLQ-C30, QLQ-OES18	90%	3, 6

Abbreviations: QLQ-C30, European Organisation for Cancer Research and Treatment general quality of life questionnaire Core 30; QLQ-OES18, European Organisation for Cancer Research and Treatment oesophageal cancer specific quality of life questionnaire Oesophageal 18; RCT, Randomized clinical trial; SF-36, Short Form (36) Health Survey 36, MFI-20, Multi-dimensional Fatigue Inventory

Table 2. Surgery, gender age and neoadjuvant therapy distributions of the patients in the included studies

References	Number of patients			Gender Male/Female		Mean age		Neoadjuvant therapy	
	Open	HMIO	TMIO	Open	MIO	Open	MIO	Open	MIO
Barbour, 2016	110	377	0	98/12	316/61	64*	64*	56/110	202/377
Hong, 2013	55	0	59	41/18	38/17	56	56	0/55	0/59
Maas, 2015	56	0	59	46/10	43/16	62*	62*	56/56	59/59
Nafteux, 2011	101	0	65	82/19	49/16	64	63	ND	ND
Parameswaran, 2013	19	31	36	15/4	47/20	64*	67, 64* ^a	17/19	27/31, 23/36
Shen, 2015	29	33	0	23/6	25/8	ND	ND	ND	ND
Wang, 2010	29	27	0	19/10	19/8	58	61	0/29	0/27
Wang, 2015	444	63	381†	358/86	362/82	56*	56*	75/444	80/444
Zeng, 2012	30, 30 ^b	0	30	19/11, 20/10 ^b	21/9	58, 63 ^b	66	0/60	0/30

†analysed as HMIO; *median; ^aTwo groups, HMIO, TMIO; ^bTwo groups, Ivor-Lewis, left transthoracic

Abbreviations: MIO, minimally invasive oesophagectomy; HMIO, hybrid minimally invasive oesophagectomy; TMIO, totally minimally invasive oesophagectomy; ND, not described.

Figure 1

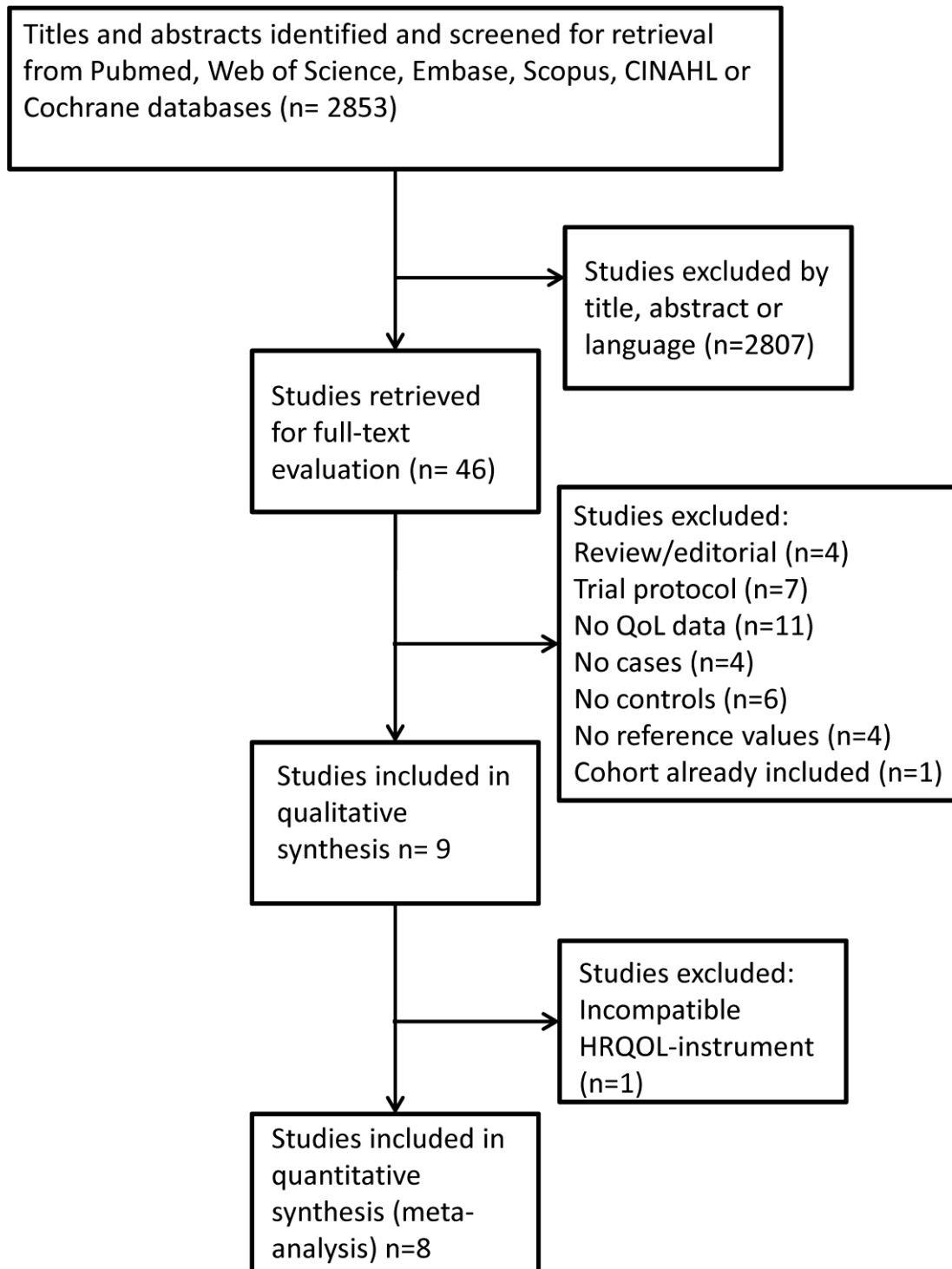
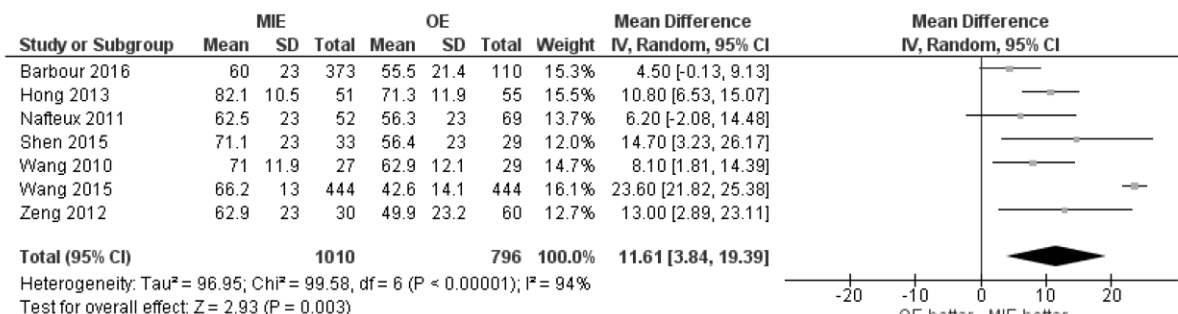
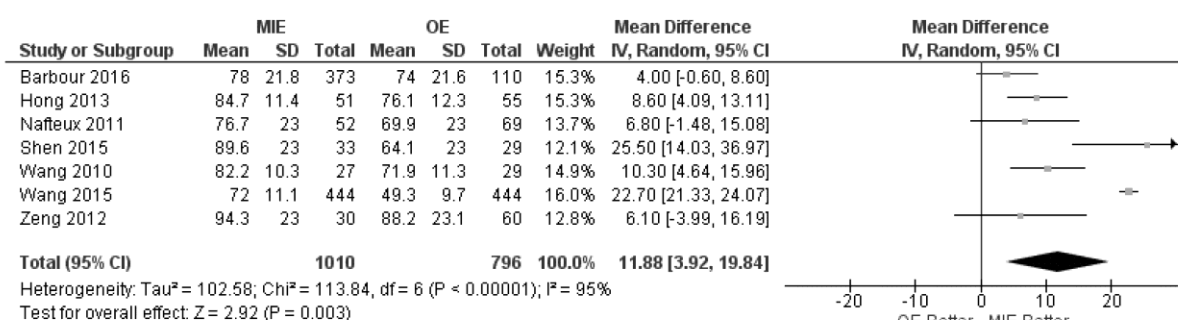


Figure 2

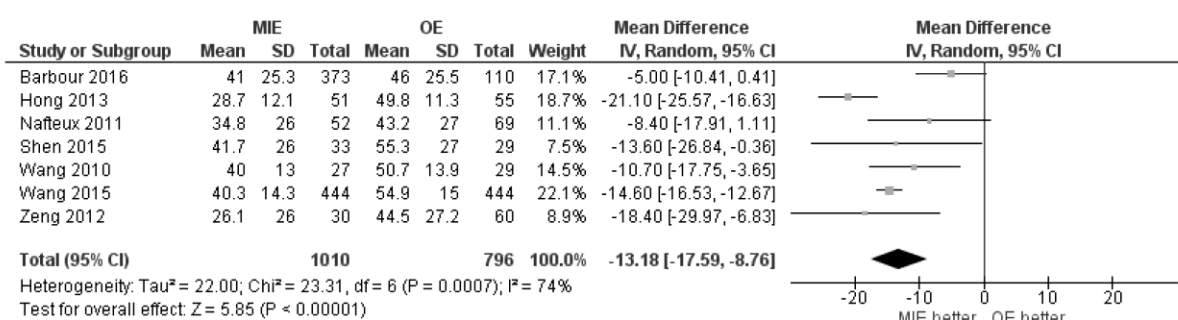
A) Global HRQOL



B) Physical function



C) Fatigue



D) Pain

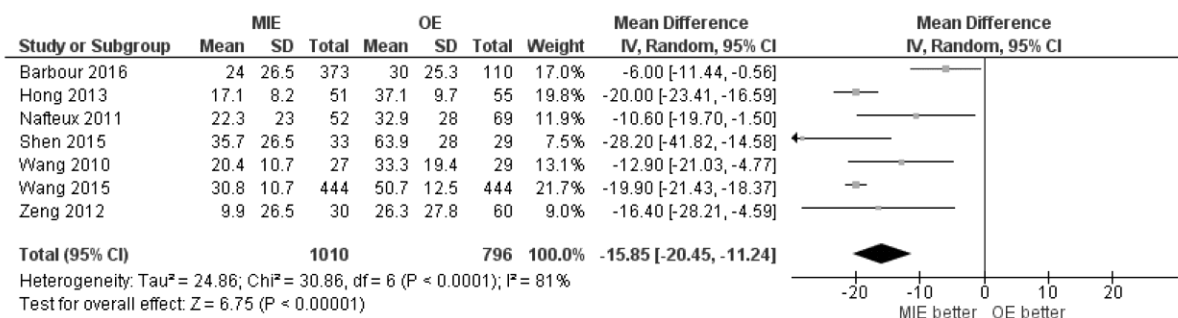
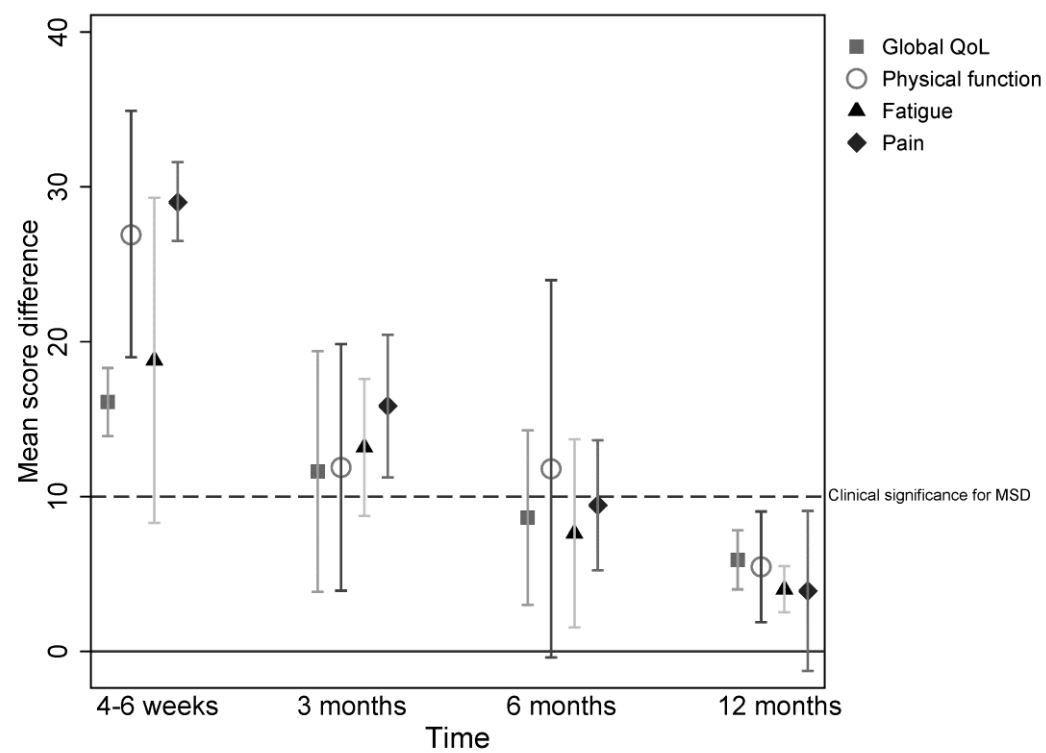
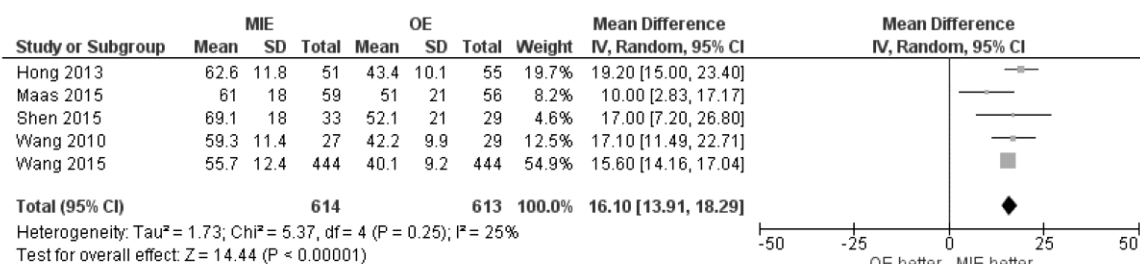


Figure 3

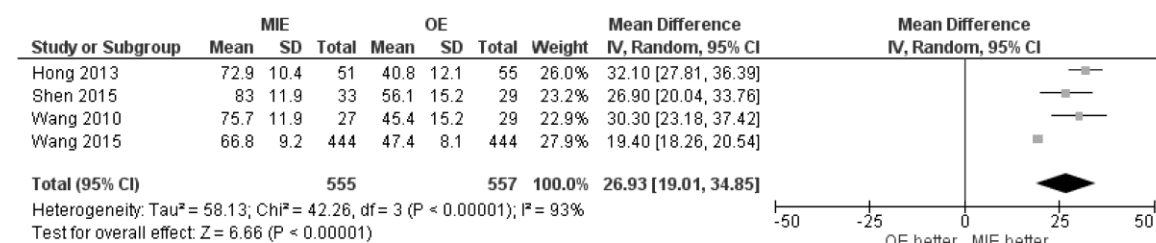


Suppl. Figure 1

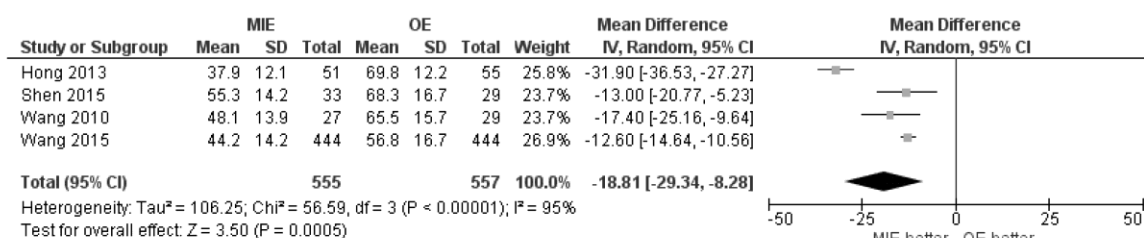
A) Global HRQOL



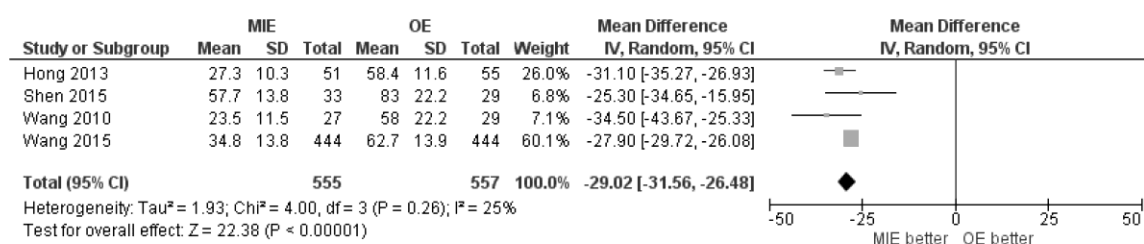
B) Physical function



C) Fatigue

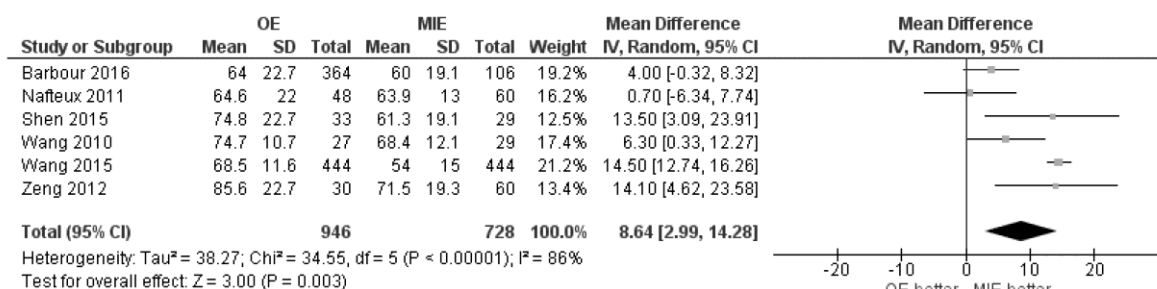


D) Pain

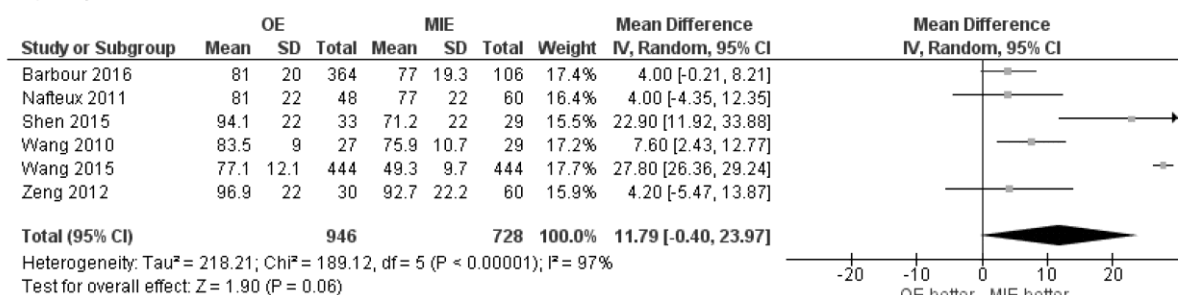


Suppl figure 2

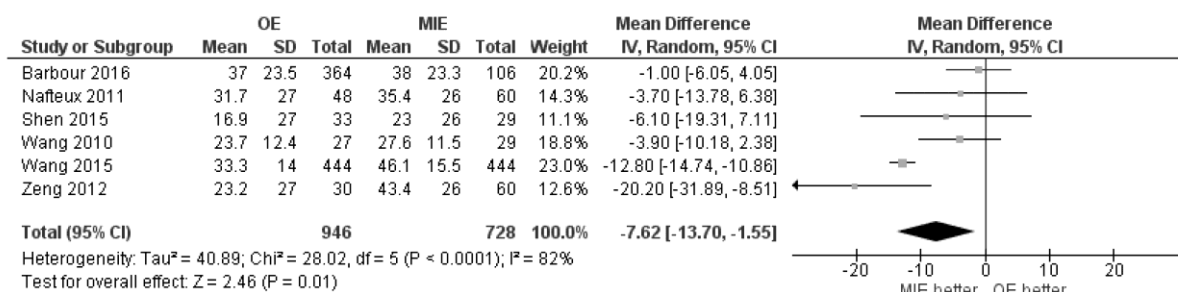
A) Global HRQOL



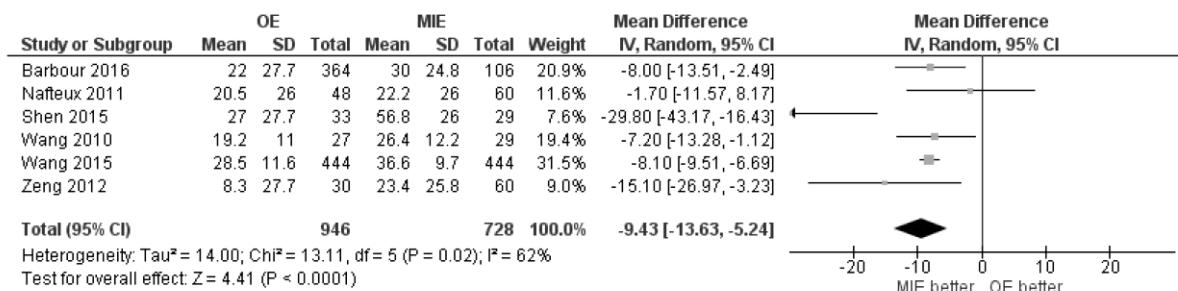
B) Physical function



C) Fatigue

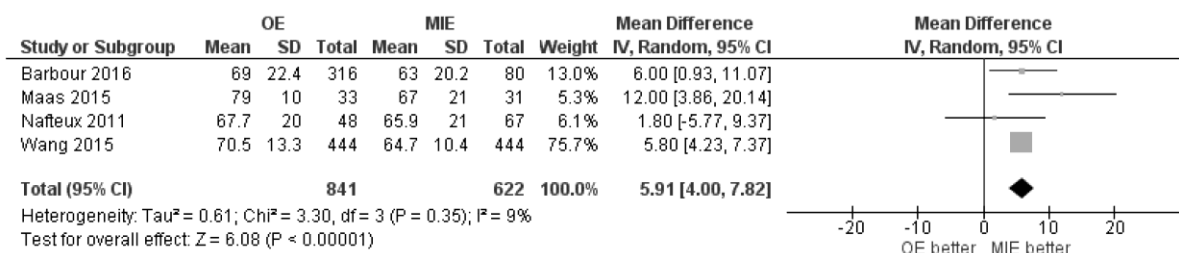


D) Pain

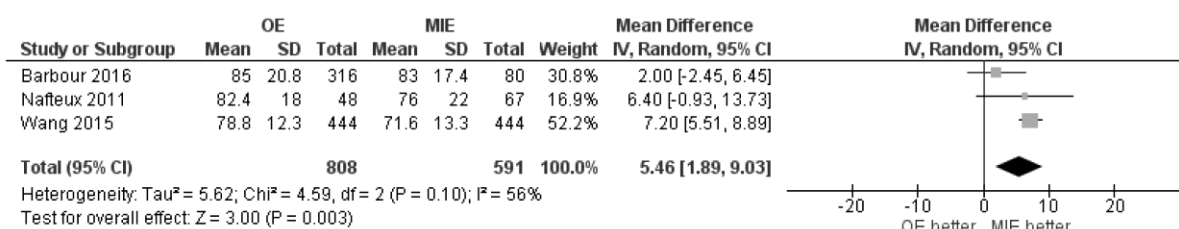


Suppl figure 3

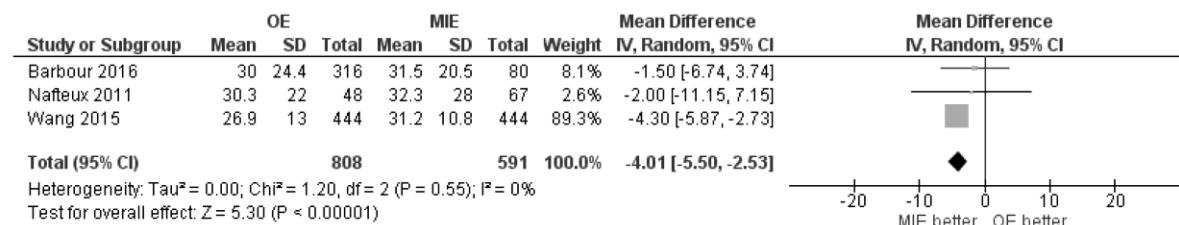
A) Global HRQOL



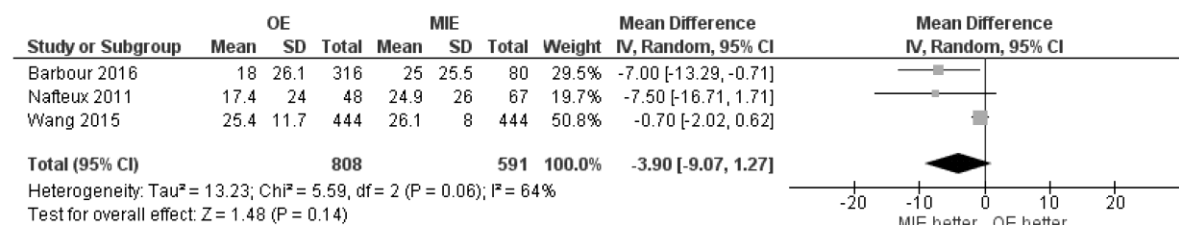
B) Physical function



C) Fatigue



D) Pain



Suppl figure 4

