Cochrane Australia

# Systematic review of evidence on the clinical effectiveness of reflexology

## Appendix D – additional results and citations for included studies

14 November 2024

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# Additional results

### Study characteristics

Study characteristics (including eligible and included participants, and the interventions evaluated) and the outcomes measured and selected from each study for inclusion in the meta-analysis are reported in Appendix E1. Details of funding, ethics approval and any other declarations of interest for each study are in Appendix E2.

### Risk of bias assessments

The overall risk of bias rating for each study included for meta-analysis is reported in the forest plots (main report). The complete risk of bias assessment for each study is reported in Appendix F. Assessments are grouped by study design (parallel-randomised trials, crossover trials, and cluster-randomised trials), then ordered alphabetically within each design by study ID. For each study, a separate risk of bias assessment was made for all comparisons and outcomes contributing to meta-analysis. If the assessment was the same for different comparisons/outcomes, only one assessment is reported (See Appendix F for details).

## D1 Pain

Results presented in this section are for the subgroup analysis, sensitivity analysis, and analyses to examine the risk of bias due to missing results.

For the outcome pain, 46 studies were included in the meta-analysis that compared reflexology to an inactive control (usual care, no intervention, sham, co-intervention given in both groups).

**Results of subgroup analysis by population group**

A subgroup analysis was performed to investigate whether there were differences in the effects between population groups (i.e. surgery, procedures, labour and childbirth, other acute pain, cancer or advanced disease, chronic musculoskeletal conditions, other chronic pain). Primarily, these were planned to explore possible explanations for any inconsistent effects if observed across studies (statistical heterogeneity).

*Assessment of heterogeneity:* While there are differences in the size of the estimated intervention effect across studies for this comparison and outcome, the effect estimate for the majority of studies in the overall analysis was above the threshold for an important improvement in pain (i.e. an SMD < -0.2). As such, the observed inconsistency is considered unimportant as it does not alter the interpretation of findings for this outcome (noting that there were serious concerns about inconsistency within some subgroups because of the higher proportion of inconsistent results).

The subgroup analyses did not explain any observed differences across studies in the direction or size of the observed effect. Results for this analysis are presented in the main report (Section 4.2, Figure 4.2.1). The test for subgroup differences was not statistically significant (P = 0.44) and the combined estimate of effect indicated an important improvement in pain for each of the population groups. Overall, there is evidence that the effects are consistent across population groups (all showing important benefit, despite variation in the magnitude of benefit).

**Results of sensitivity analyses**

**Table D1.1** presents results for the original analysis (all studies, random effects model) and two sensitivity analyses. These sensitivity analyses investigate:

1. whether the combined estimate is sensitive to the assumptions that were made to enable inclusion of results in the meta-analysis, specifically transforming or imputing statistics, and including change scores (change from baseline) when post-intervention (final) values (and their standard deviations) were unavailable; and
2. whether the combined effect differs when estimated from a fixed effect model, providing evidence of small study effects (which may be due to true differences in the effects in small studies or may suggest non-reporting bias).

The combined estimate of effect was similar in the original analysis and the sensitivity analyses removing studies for which transforming / imputing statistics or using change scores was necessary. This indicates that the result was robust to the assumptions required to include these results.

**Table D1.1. Sensitivity analyses for pain outcome**

| Sensitivity analysis | Purpose of sensitivity analysis | No trials | Original effect (95% CI) | No trials | Sensitivity analysis effect |
|---|---|---|---|---|---|
| No imputation, transformations or change scores [1] | Investigate robustness of MA effect | 46 | SMD -1.02(-1.26 to -0.78); $I^2$ = 89% | 36 | SMD -1.09 (-1.38 to -0.81); $I^2$ = 90% |
| Fixed effect analysis | Investigate small study effects (bias due to missing results) | | | 46 | SMD -0.82 (-0.89 to -0.75); $I^2$ = 88% |

[1] This analysis was limited to trials that (a) reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals, and (b) had post-intervention (final) values available.

*Abbreviations*. MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

**Bias due to missing results from the meta-analysis**

The combined effect estimated from the fixed effect model (SMD -0.82) was smaller than from the random effects model (SMD -1.02) (Table D1.1), which may suggest small study effects arising from selective non-reporting of unfavourable results (Table D1.1). The contour-enhanced funnel plot in Figure D1.1 suggests that there could be missing studies that show effects favouring the control, and nonsignificant effects in general (i.e. the plot is asymmetric, missing studies to the right of the line of no effect (SMD 0) where we would expect results for some small studies, most notably in the darker grey shaded areas where nonsignificant results appear; in addition only a minority of studies to the left of the line of no effect are non-significant).

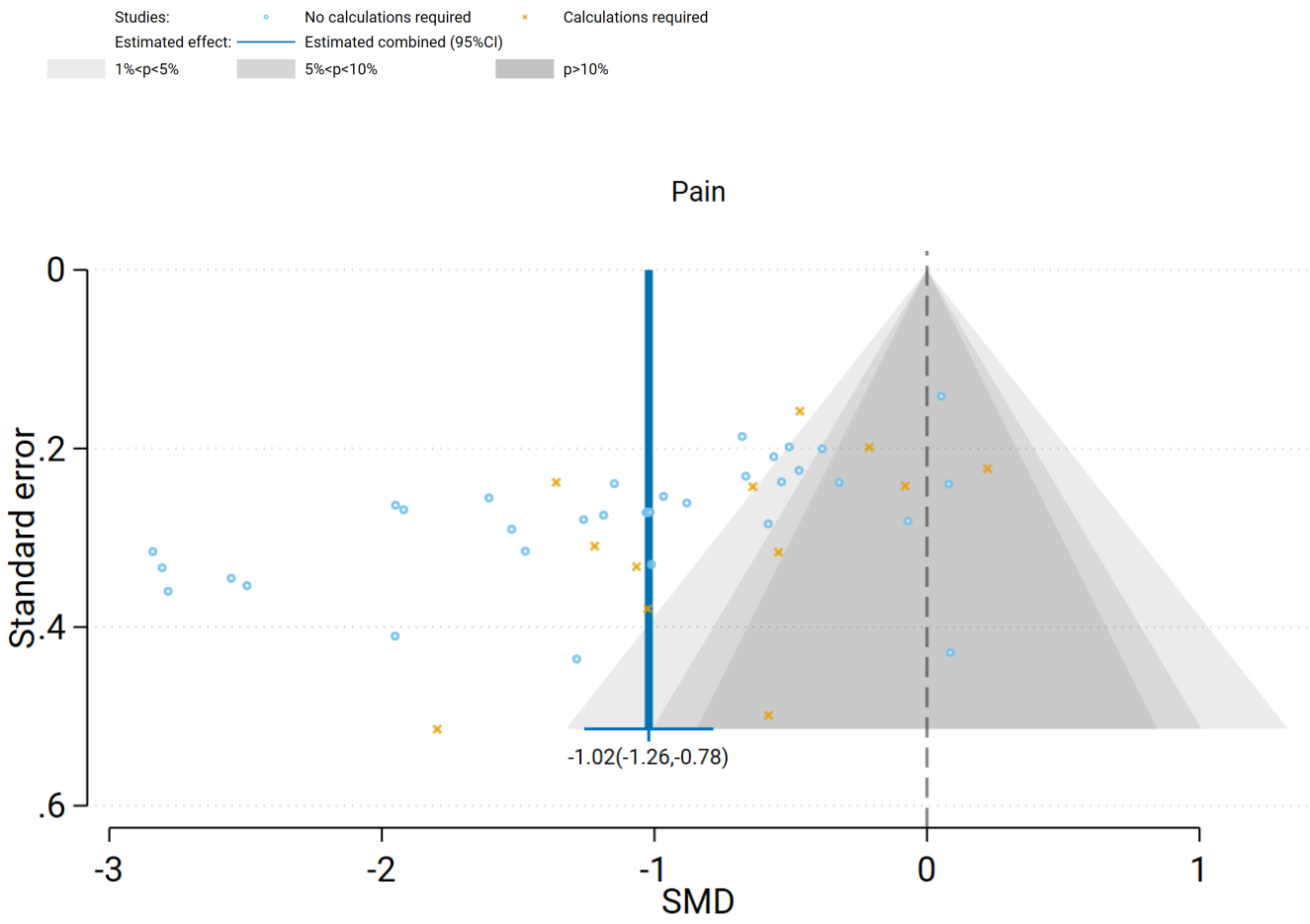


**Fig D1.1** | Contour enhanced funnel plot of estimates of SMD versus their standard errors for comparison of the effect of reflexology (any mode) versus inactive control (usual care, no intervention, sham, co-intervention given in both groups) on pain. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

## D2 Sleep

Results presented in this section are for the subgroup analysis, sensitivity analysis, and analyses to examine the risk of bias due to missing results.

For the outcome sleep, 12 studies were included in the meta-analysis that compared reflexology to an inactive control (usual care, no intervention, sham, co-intervention given in both groups).

### Results of subgroup analysis by population group

A subgroup analysis was performed to investigate whether there were differences in the effects between population groups (i.e. surgery, hospitalisation, sleep disruption, cancer and advanced disease). Primarily, these were planned to explore possible explanations for any inconsistent effects if observed across studies (statistical heterogeneity).

*Assessment of heterogeneity:* While there are differences in the size of the estimated intervention effect across studies for this comparison and outcome, the effect estimate for all 12 studies was above the threshold for an important improvement in sleep quality (i.e. an SMD > 0.2). As such, the observed inconsistency is considered unimportant as it does not alter the interpretation of findings for this outcome.

The subgroup analyses may explain some of the observed differences across studies in the direction or size of the observed effect. Results for this analysis are presented in the main report (Section 4.4, Figure 4.4.1). The test for subgroup differences was statistically significant (P = 0.045), but the combined estimate of effect indicated an important improvement in sleep for each of the population groups. Overall, there is evidence that the effects are consistent across population groups (all showing important benefit, despite variation in the magnitude of benefit).

### Results of sensitivity analyses

**Table D2.1** presents results for the original analysis (all studies, random effects model) and two sensitivity analyses. These sensitivity analyses investigate:

1. whether the combined estimate is sensitive to the assumptions that were made to enable inclusion of results in the meta-analysis, specifically transforming or imputing statistics, and including change scores (change from baseline) when post-intervention (final) values (and their standard deviations) were unavailable; and
2. whether the combined effect differs when estimated from a fixed effect model, providing evidence of small study effects (which may be due to true differences in the effects in small studies or may suggest non-reporting bias).

The first sensitivity analysis was not required because we did not need to calculate / impute statistics or use change scores for any studies in this meta-analysis.

**Table D2.1. Sensitivity analyses for sleep outcome**

| Sensitivity analysis | Purpose of sensitivity analysis | No trials | Original effect (95% CI) | No trials | Sensitivity analysis effect |
|---|---|---|---|---|---|
| No imputation, transformations or change scores [1] | Investigate robustness of MA effect | 12 | SMD 1.37 (0.88 to 1.87); I2 = 87% | | Not required (no imputation, transformation, or change scores) |
| Fixed effect analysis | Investigate small study effects (bias due to missing results) | | | 12 | SMD 1.21 (1.06 to 1.37); I2 = 85% |

[1] This analysis was limited to trials that (a) reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals, and (b) had post-intervention (final) values available.

*Abbreviations*. MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

### Bias due to missing results from the meta-analysis

The combined effect estimated from the fixed effect model (SMD 1.21) was similar to that from the random effects model (SMD 1.37) (Table D2.1); both indicated an improvement in sleep quality greater than the threshold for an important effect. The contour-enhanced funnel plot in Figure D2.1 suggests that there could be missing studies which show effects favouring the control, and nonsignificant effects in general (i.e. the plot is asymmetric, missing studies to the left of the line of no effect (SMD 0) where we would expect results for some small studies, most notably in the darker

grey shaded areas where nonsignificant results appear; in addition only a minority of studies to the right of the line of no effect are non-significant).

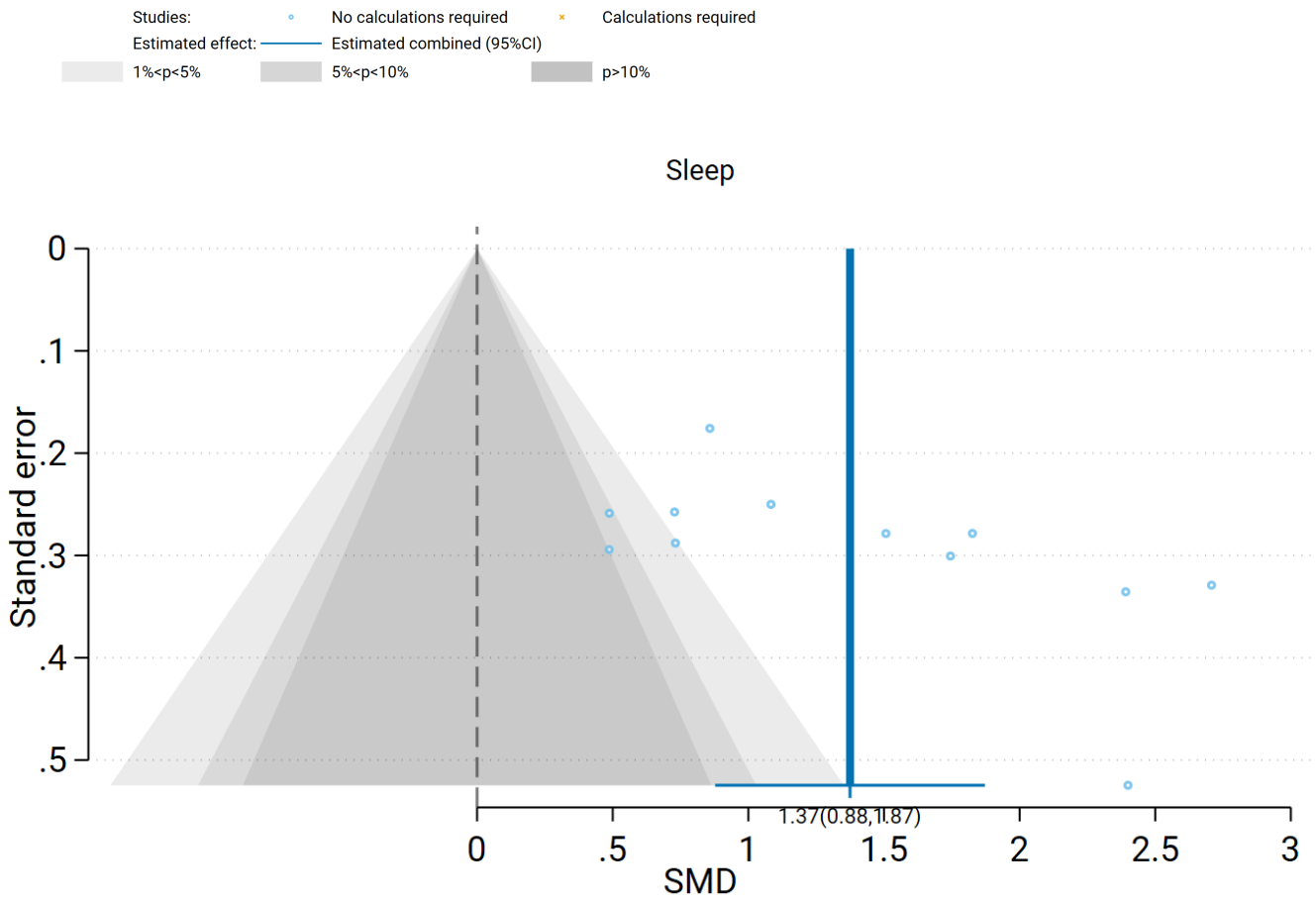


**Fig D2.1** | Contour enhanced funnel plot of estimates of SMD versus their standard errors for comparison of the effect of reflexology versus inactive control (usual care, no intervention, placebo) on sleep quality. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

## D3 Fatigue

Results presented in this section are for the subgroup analysis, sensitivity analysis, and analyses to examine the risk of bias due to missing results.

For the outcome fatigue, 19 studies were included in the meta-analysis that compared reflexology to an inactive control (usual care, no intervention, sham, co-intervention given in both groups).

**Results of subgroup analysis by population group**

A subgroup analysis was performed to investigate whether there were differences in the effects between population groups (i.e. cancer and advanced disease, chronic musculoskeletal conditions, other chronic conditions, pregnancy). Primarily, these were planned to explore possible explanations for any inconsistent effects if observed across studies (statistical heterogeneity).

*Assessment of heterogeneity:* There are differences in the size of the estimated intervention effect across studies for this comparison and outcome that suggest inconsistent effects. While the effect estimate for the majority of studies was above the threshold for an important improvement in fatigue (i.e. an SMD < - 0.2), about ¼ of studies in the analysis showed trivial effects (an SMD between -0.2 and 0.2). As such, the observed inconsistency is considered serious for the overall analysis and requires explanation to understand the factors that may influence whether reflexology has a beneficial or trivial effect.

The subgroup analyses did not explain the observed differences across studies in the direction or size of the observed effect. Results for this analysis are presented in the main report (Section 4.4, Figure 4.4.1). The test for subgroup differences was not statistically significant (P = 0.254) and there was inconsistency in the effects observed across studies within all population groups, which we considered serious for two groups (chronic musculoskeletal conditions, pregnancy). Overall, there is evidence that the effects are inconsistent across population groups (some showing important benefit, others showing trivial effects).

**Results of sensitivity analyses**

**Table D3.1** presents results for the original analysis (all studies, random effects model) and two sensitivity analyses. These sensitivity analyses investigate:

1. whether the combined estimate is sensitive to the assumptions that were made to enable inclusion of results in the meta-analysis, specifically transforming or imputing statistics, and including change scores (change from baseline) when post-intervention (final) values (and their standard deviations) were unavailable; and
2. whether the combined effect differs when estimated from a fixed effect model, providing evidence of small study effects (which may be due to true differences in the effects in small studies or may suggest non-reporting bias).

The combined estimate of effect was similar in the original analysis and the sensitivity analyses removing studies for which transforming / imputing statistics or using change scores was necessary. This indicates that the result was robust to the assumptions required to include these results.

**Table D3.1. Sensitivity analyses for fatigue outcome**

| Sensitivity analysis | Purpose of sensitivity analysis | No trials | Original effect (95% CI) | No trials | Sensitivity analysis effect |
|---|---|---|---|---|---|
| No imputation, transformations or change scores [1] | Investigate robustness of MA effect | 19 | SMD -0.85 (-1.20 to -0.50); I2 = 89% | 17 | SMD -0.85 (-1.25 to -0.45); I2 = 91% |
| Fixed effect analysis | Investigate small study effects (bias due to missing results) | | | 20 | SMD -0.61 (-0.72 to -0.51); I2 = 87% |

[1] This analysis was limited to trials that (a) reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals, and (b) had post-intervention (final) values available.

*Abbreviations*. MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

**Bias due to missing results from the meta-analysis**

The combined effect estimated from the fixed effect model (SMD -0.61) was smaller than from the random effects model (SMD -0.85) (Table D3.1), which may suggest small study effects arising from selective non-reporting of unfavourable results (Table D3.1). The contour-enhanced funnel plot in Figure D3.1 suggests that there could be missing studies which show effects favouring the control, and nonsignificant effects in general (i.e. the plot is asymmetric, missing studies to the right of the line of no effect (SMD 0) where we would expect results for some small studies, most notably in the darker grey shaded areas where nonsignificant results appear; in addition only a minority of studies to the left of the line of no effect are non-significant).

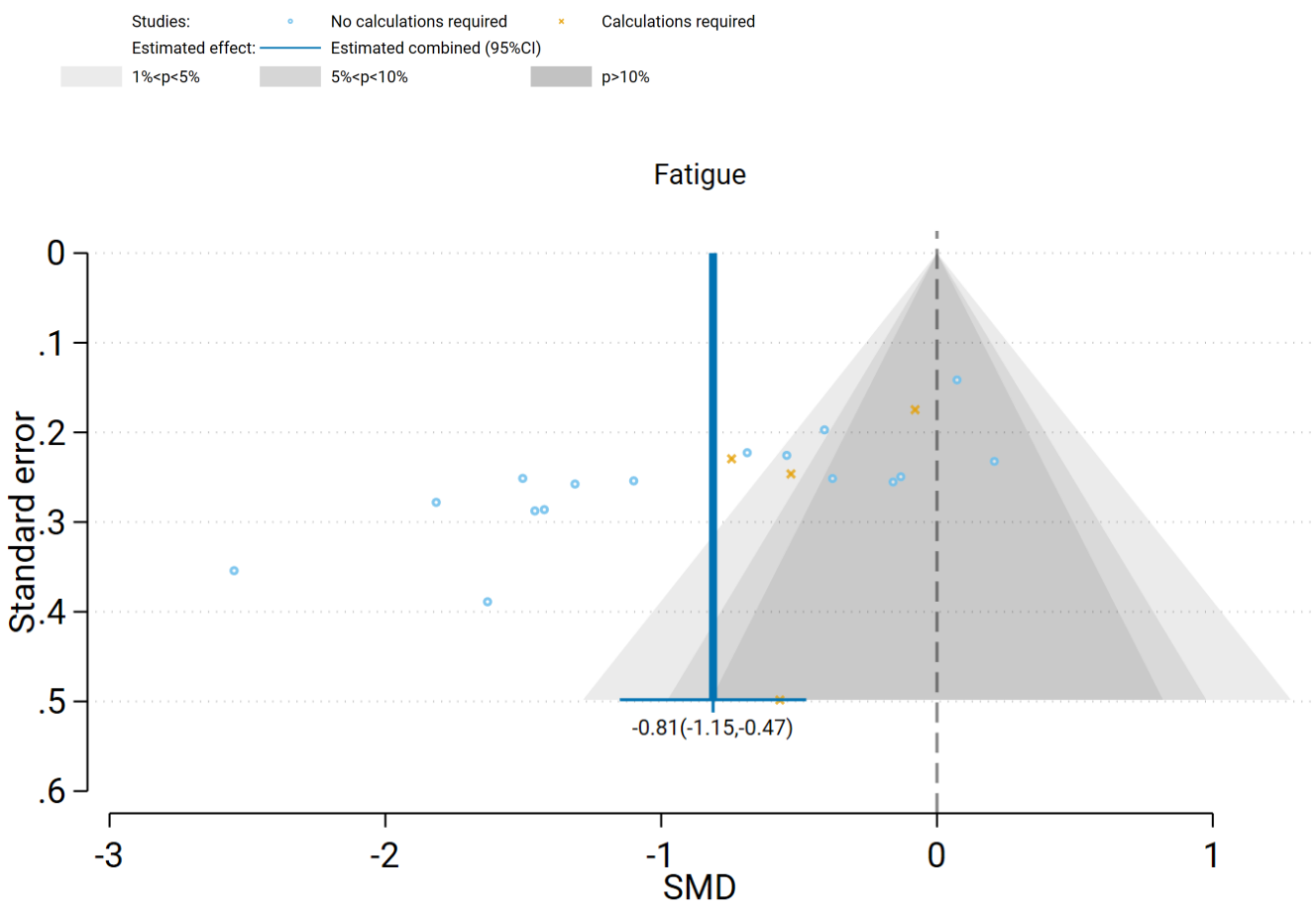


**Fig D3.1** | Contour enhanced funnel plot of estimates of SMD versus their standard errors for the comparison of the effect of reflexology versus inactive control (usual care, no intervention, placebo) on fatigue. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

## D4 Emotional functioning and mental health

Results presented in this section are for the subgroup analysis, sensitivity analysis, and analyses to examine the risk of bias due to missing results.

For the outcome emotional functioning and mental health, 40 studies were included in the meta-analysis that compared reflexology to an inactive control (usual care, no intervention, sham, co-intervention given in both groups).

**Results of subgroup analysis by population group**

A subgroup analysis was performed to investigate whether there were differences in the effects between population groups (i.e. surgery, procedures, hospitalisation, labour and childbirth, mental distress, cancer and advanced disease, mental disorders, dementia). Primarily, these were planned to explore possible explanations for any inconsistent effects if observed across studies (statistical heterogeneity).

*Assessment of heterogeneity:* There are differences in the size of the estimated intervention effect across studies for this comparison and outcome that suggest inconsistent effects. While the effect estimate for the majority of studies was above the threshold for an important improvement in emotional functioning and mental health (i.e. an SMD < - 0.2), more than ¼ of studies in the analysis showed trivial effects (an SMD between -0.2 and 0.2) or effects favouring the control. As such, the observed inconsistency is considered serious for the overall analysis and requires explanation to understand the factors that may influence whether reflexology has a beneficial or trivial effect.

The subgroup analyses did not explain the observed differences across studies in the direction or size of the observed effect. Results for this analysis are presented in the main report (Section 4.5, Figure 4.5.1). The test for subgroup

differences was not statistically significant (P = 0.1) and there was inconsistency in the effects observed across studies within the majority population groups, which we considered serious for one group (cancer and advanced disease). Overall, there is evidence that the effects are inconsistent across population groups (some showing important benefit, others showing trivial effects).

**Results of sensitivity analyses**

**Table D4.1** presents results for the original analysis (all studies, random effects model) and two sensitivity analyses. These sensitivity analyses investigate:

1. whether the combined estimate is sensitive to the assumptions that were made to enable inclusion of results in the meta-analysis, specifically transforming or imputing statistics, and including change scores (change from baseline) when post-intervention (final) values (and their standard deviations) were unavailable; and
2. whether the combined effect differs when estimated from a fixed effect model, providing evidence of small study effects (which may be due to true differences in the effects in small studies or may suggest non-reporting bias).

The combined estimate of effect was similar in the original analysis and the sensitivity analyses removing studies for which transforming / imputing statistics or using change scores was necessary. This indicates that the result was robust to the assumptions required to include these results.

**Table D4.1. Sensitivity analyses for emotional functioning and mental health outcome**

| Sensitivity analysis | Purpose of sensitivity analysis | No trials | Original effect (95% CI) | No trials | Sensitivity analysis effect |
|---|---|---|---|---|---|
| No imputation, transformations or change scores [1] | Investigate robustness of MA effect | 40 | SMD -0.69 (-0.93 to -0.44); I2 = 91% | 31 | SMD -0.62 (-0.90 to -0.35); I2 = 89% |
| Fixed effect analysis | Investigate small study effects (bias due to missing results) | | | 40 | SMD -0.57 (-0.64 to -0.50); I2 = % |

[1] This analysis was limited to trials that (a) reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals, and (b) had post-intervention (final) values available.

*Abbreviations*. MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

**Bias due to missing results from the meta-analysis**

The combined effect estimated from the fixed effect model (SMD -0.57) was smaller than from the random effects model (SMD -0.69) (Table D4.1), which may suggest small study effects arising from selective non-reporting of unfavourable results (Table D4.1). The contour-enhanced funnel plot in Figure D5.1 suggests that there could be missing studies which show effects favouring the control, especially nonsignificant effects (i.e. the plot is asymmetric, missing studies to the right of the line of no effect (SMD 0) where we would expect results for some small studies, most notably in the darker grey shaded areas where nonsignificant results appear; in addition only a minority of studies to the left of the line of no effect are non-significant).

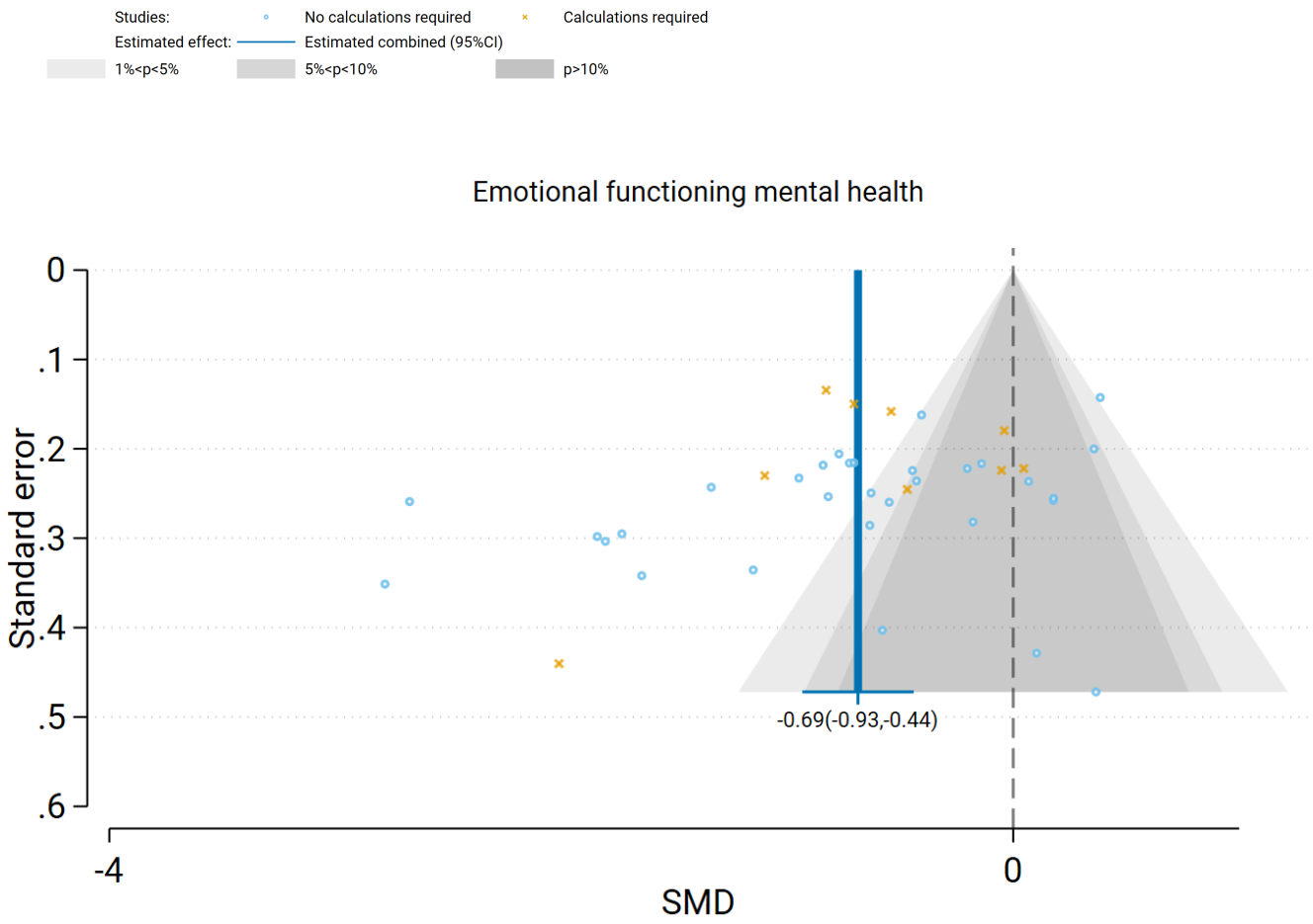


**Fig D4.1** | Contour enhanced funnel plot of estimates of SMD versus their standard errors for comparison of the effect of reflexology versus inactive control (usual care, no intervention, placebo) on emotional functioning and mental health. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

## D5 Health-related quality of life (HR-QoL)

Results presented in this section are for the subgroup analysis, sensitivity analysis, and analyses to examine the risk of bias due to missing results.

For the outcome health-related quality of life, 20 studies were included in the meta-analysis that compared reflexology to an inactive control (usual care, no intervention, sham, co-intervention given in both groups).

**Results of subgroup analysis by population group**

A subgroup analysis was performed to investigate whether there were differences in the effects between population groups (i.e. cancer and advanced disease, other chronic conditions). Primarily, these were planned to explore possible explanations for any inconsistent effects if observed across studies (statistical heterogeneity).

*Assessment of heterogeneity:* There are differences in the size of the estimated intervention effect across studies for this comparison and outcome that suggest inconsistent effects. Effect estimate vary importantly with about half the studies showing an effect above the threshold for an important improvement in health-related quality of life (i.e. an SMD > 0.2), while the other studies in the analysis showed trivial effects (an SMD between -0.2 and 0.2). As such, the observed inconsistency is considered serious for the overall analysis and requires explanation to understand the factors that may influence whether reflexology has a beneficial or trivial effect.

The subgroup analyses did not explain the observed differences across studies in the direction or size of the observed effect (see Figure 4.6.1). Results for this analysis are presented in the main report (Section 4.6, Figure 4.6.1). The test for subgroup differences was not statistically significant (P = 0.95) and there was serious inconsistency in the effects

observed across studies within the both population groups, which we considered serious for one group (cancer and advanced disease). Overall, there is evidence that the effects are inconsistent across population groups (some showing important benefit, others showing trivial effects).

**Results of sensitivity analyses**

**Table D5.1** presents results for the original analysis (all studies, random effects model) and two sensitivity analyses. These sensitivity analyses investigate:

1. whether the combined estimate is sensitive to the assumptions that were made to enable inclusion of results in the meta-analysis, specifically transforming or imputing statistics, and including change scores (change from baseline) when post-intervention (final) values (and their standard deviations) were unavailable; and
2. whether the combined effect differs when estimated from a fixed effect model, providing evidence of small study effects (which may be due to true differences in the effects in small studies or may suggest non-reporting bias).

The combined estimate of effect was similar in the original analysis and the sensitivity analyses removing studies for which transforming / imputing statistics or using change scores was necessary. This indicates that the result was robust to the assumptions required to include these results.

**Table D5.1. Sensitivity analyses for HR-QoL outcome**

| Sensitivity analysis | Purpose of sensitivity analysis | No trials | Original effect (95% CI) | No trials | Sensitivity analysis effect |
|---|---|---|---|---|---|
| No imputation, transformations or change scores [1] | Investigate robustness of MA effect | 20 | SMD 0.53 (0.19 to 0.86); I2 = 88% | 15 | SMD 0.58 (0.16 to 1.01); I2 = 90% |
| Fixed effect analysis | Investigate small study effects (bias due to missing results) | | | 20 | SMD 0.33 (0.23 to 0.44); I2 = 84% |

[1] This analysis was limited to trials that (a) reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals, and (b) had post-intervention (final) values available.

*Abbreviations*. MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

**Bias due to missing results from the meta-analysis**

The combined effect estimated from the fixed effect model (SMD 0.33) was smaller than from the random effects model (SMD 0.53) (Table D5.1), which may suggest small study effects arising from selective non-reporting of unfavourable results. The contour-enhanced funnel plot in Figure D5.1 suggests that there could be missing studies which show effects favouring the control, especially nonsignificant effects (i.e. the plot is asymmetric, missing studies to the left of the line of no effect (SMD 0) where we would expect results for some small studies, most notably in the darker grey shaded areas where nonsignificant results appear).

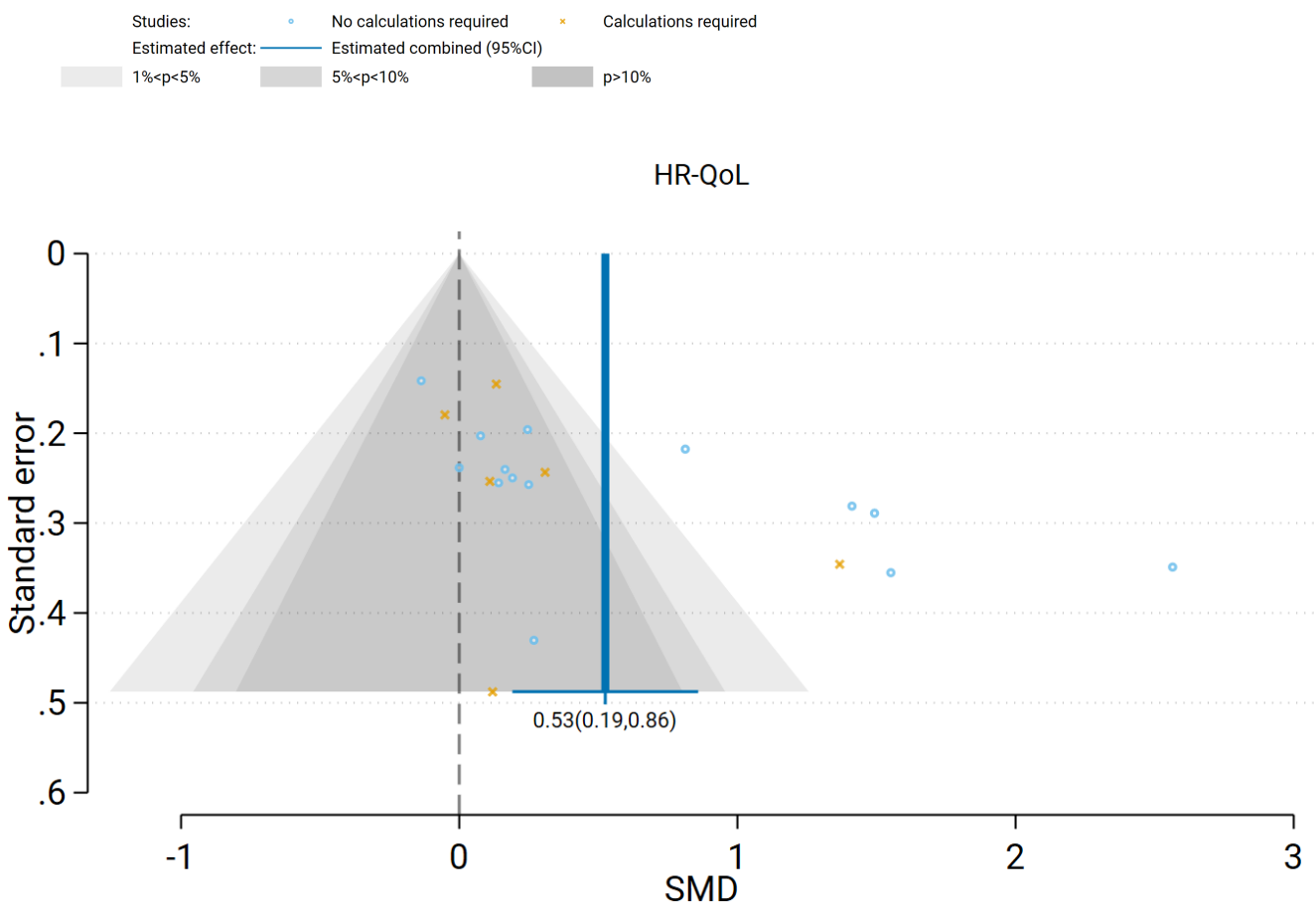


**Fig D5.1** | Contour enhanced funnel plot of estimates of SMD versus their standard errors for comparison of the effect of reflexology versus inactive control (usual care, no intervention, placebo) on HR-QoL. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

## D6 Physical function

Results presented in this section are for the subgroup analysis, sensitivity analysis, and analyses to examine the risk of bias due to missing results.

For the outcome physical function, 10 studies were included in the meta-analysis that compared reflexology to an inactive control (usual care, no intervention, sham, co-intervention given in both groups).

**Results of subgroup analysis by population group**

A subgroup analysis was performed to investigate whether there were differences in the effects between population groups (i.e. cancer and advanced disease, chronic musculoskeletal conditions, other chronic conditions). Primarily, these were planned to explore possible explanations for any inconsistent effects if observed across studies (statistical heterogeneity).

*Assessment of heterogeneity:* While there are differences in the size of the estimated intervention effect across studies for this comparison and outcome, the confidence intervals for the majority of studies were overlapping suggesting that effects across studies were compatible. As such, the observed inconsistency is considered not serious as it does not alter the interpretation of findings for this outcome (the confidence interval for most studies indicated results compatible with benefit and little to no difference/harm).

The subgroup analyses did not explain any observed differences across studies in the direction or size of the observed effect. Results for this analysis are presented in the main report (Section 4.7, Figure 4.7.1). The test for subgroup differences was not statistically significant (P = 0.68) and effects within the population groups were inconsistent (serious for cancer and advanced disease).

**Results of sensitivity analyses**

**Table D6.1** presents results for the original analysis (all studies, random effects model) and two sensitivity analyses. These sensitivity analyses investigate:

1. whether the combined estimate is sensitive to the assumptions that were made to enable inclusion of results in the meta-analysis, specifically transforming or imputing statistics, and including change scores (change from baseline) when post-intervention (final) values (and their standard deviations) were unavailable; and
2. whether the combined effect differs when estimated from a fixed effect model, providing evidence of small study effects (which may be due to true differences in the effects in small studies or may suggest non-reporting bias).

The combined estimate of effect was smaller in the original analysis (SMD 0.60) compared to the sensitivity analyses removing studies for which transforming / imputing statistics or using change scores was necessary, however both indicated effects above the threshold for an important improvement in physical function. This indicates that the result was robust to the assumptions required to include these results.

**Table D6.1. Sensitivity analyses for physical function outcome**

| Sensitivity analysis | Purpose of sensitivity analysis | No trials | Original effect (95% CI) | No trials | Sensitivity analysis effect |
|---|---|---|---|---|---|
| No imputation, transformations or change scores [1] | Investigate robustness of MA effect | 10 | SMD 0.60 (-0.02 to 1.22); I2 = 92% | 7 | SMD 0.74 (-0.19 to 1.68); I2 = 94% |
| Fixed effect analysis | Investigate small study effects (bias due to missing results) | | | 10 | SMD 0.34 (0.20 to 0.48); I2 = % |

[1] This analysis was limited to trials that (a) reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals, and (b) had post-intervention (final) values available.

*Abbreviations*. MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

**Bias due to missing results from the meta-analysis**

The combined effect estimated from the fixed effect model (SMD 0.34) was smaller than from the random effects model (SMD 0.60) (Table D6.1). While the fixed effect estimate is still above threshold for an important difference in physical function, this may suggest small study effects arising from selective non-reporting of unfavourable results. The contour-enhanced funnel plot in Figure D6.1 suggests that there could be missing studies which show effects favouring the control (i.e. the plot is asymmetric, missing studies to the left of the line of no effect (SMD 0) where we would expect results for some small studies, most notably in the darker grey shaded areas where nonsignificant results appear). However, there are a comparatively small number of studies in this analysis.

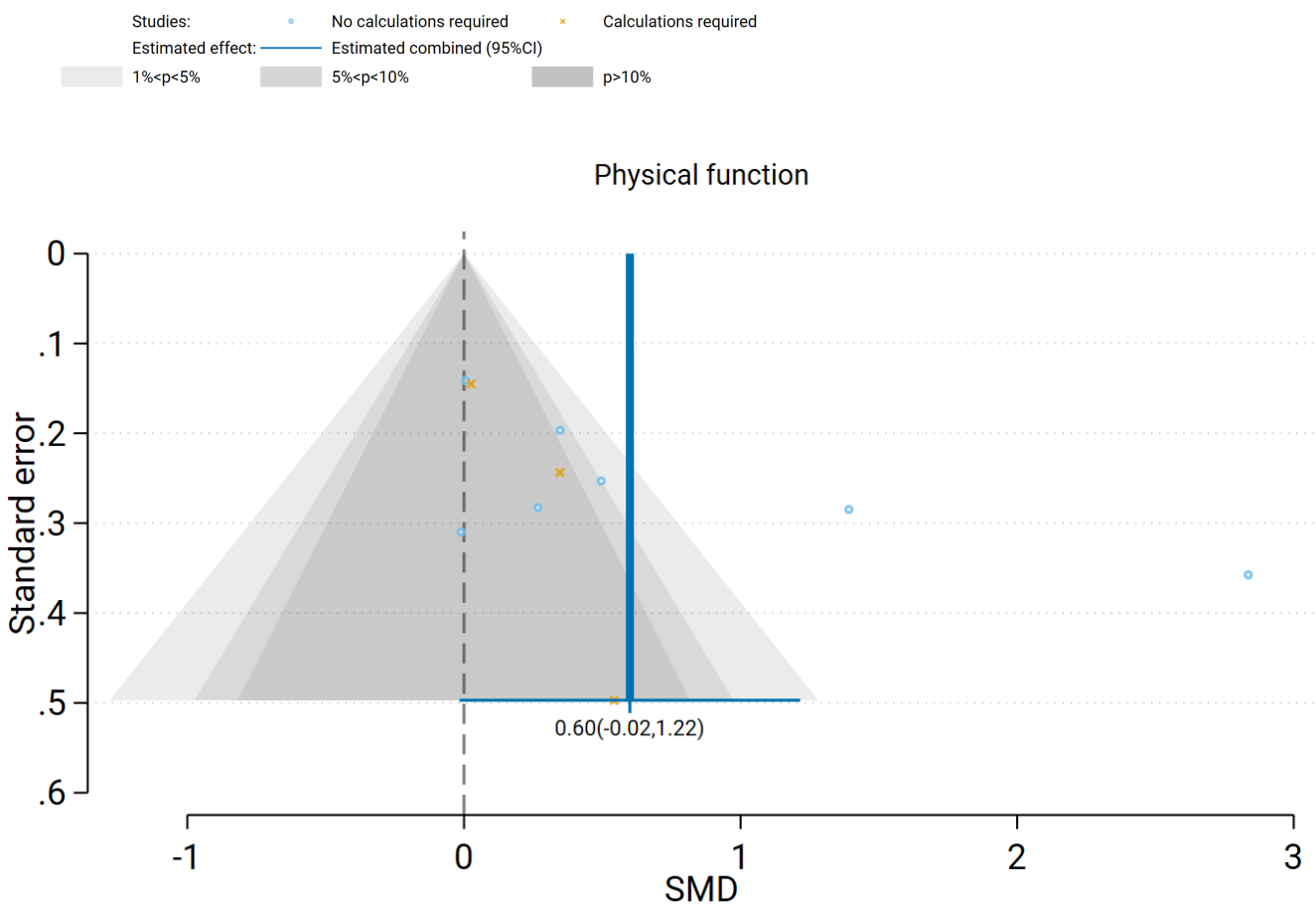


**Fig D6.1**| Contour enhanced funnel plot of estimates of SMD versus their standard errors for comparison of the effect of reflexology versus inactive control (usual care, no intervention, sham, co-intervention given in both groups) on physical function. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

## D7 Global symptoms

Results presented in this section are for the subgroup analysis, sensitivity analyses, and analyses to examine the risk of bias due to missing results.

For the outcome global symptoms, 18 studies were included in the meta-analysis for the comparison of reflexology to an inactive control (usual care, no intervention, sham, co-intervention given in both groups).

**Results of subgroup analysis by population group**

A subgroup analysis was performed to investigate whether there were differences in the effects between population groups (i.e. cancer and advanced disease, other chronic conditions, chronic respiratory conditions). Primarily, these were planned to explore possible explanations for any inconsistent effects if observed across studies (statistical heterogeneity).

*Assessment of heterogeneity:* There are differences in the size of the estimated intervention effect across studies for this comparison and outcome that suggest inconsistent effects. Effect estimate vary importantly with the majority of studies showing an effect above the threshold for an important improvement in global symptoms (i.e. an SMD < - 0.2), while the other studies in the analysis showed trivial effects (an SMD between -0.2 and 0.2). As such, the observed inconsistency is considered serious for the overall analysis and requires explanation to understand the factors that may influence whether reflexology has a beneficial or trivial effect.

The subgroup analyses suggested the population group may explain some of the observed differences across studies in the size of the observed effect (see Figure 4.8.1). Results for this analysis are presented in the main report (Section 4.8,

Figure 4.8.1). The test for subgroup differences was statistically significant (P = 0.014) which was most likely due to the very large effects observed in the 'other chronic conditions' subgroup. However, there was inconsistency in the effects observed across studies within the population groups (although not rated as serious).

**Results of sensitivity analyses**

**Table D7.1** presents results for the original analysis (all studies, random effects model) and two sensitivity analyses. These sensitivity analyses investigate:

1. whether the combined estimate is sensitive to the assumptions that were made to enable inclusion of results in the meta-analysis, specifically transforming or imputing statistics, and including change scores (change from baseline) when post-intervention (final) values (and their standard deviations) were unavailable; and
2. whether the combined effect differs when estimated from a fixed effect model, providing evidence of small study effects (which may be due to true differences in the effects in small studies or may suggest non-reporting bias).

The combined estimate of effect was similar in the original analysis and the sensitivity analyses removing studies for which transforming / imputing statistics or using change scores was necessary. This indicates that the result was robust to the assumptions required to include these results.

**Table D7.1. Sensitivity analyses for global symptoms outcome**

| Sensitivity analysis | Purpose of sensitivity analysis | No trials | Original effect (95% CI) | No trials | Sensitivity analysis effect |
|---|---|---|---|---|---|
| No imputation, transformations or change scores [1] | Investigate robustness of MA effect | 18 | SMD -0.96 (-1.37 to -0.55); I2 = 89% | 15 | SMD -1.02 (-1.49 to -0.55); I2 = 89% |
| Fixed effect analysis | Investigate small study effects (bias due to missing results) | | | | SMD -0.73 (-0.86 to -0.61); I2 = 88% |

[1] This analysis was limited to trials that (a) reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals, and (b) had post-intervention (final) values available.

*Abbreviations*. MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

**Bias due to missing results from the meta-analysis**

The combined effect estimated from the fixed effect model (SMD -0.73) was smaller than from the random effects model (SMD -0.96) (Table D7.1), which may suggest small study effects arising from selective non-reporting of unfavourable results. The contour-enhanced funnel plot in Figure D7.1 suggests that there could be missing studies which show effects favouring the control (i.e. the plot is asymmetric, missing studies to the left of the line of no effect (SMD 0) where we would expect results for some small studies, most notably in the darker grey shaded areas where nonsignificant results appear).

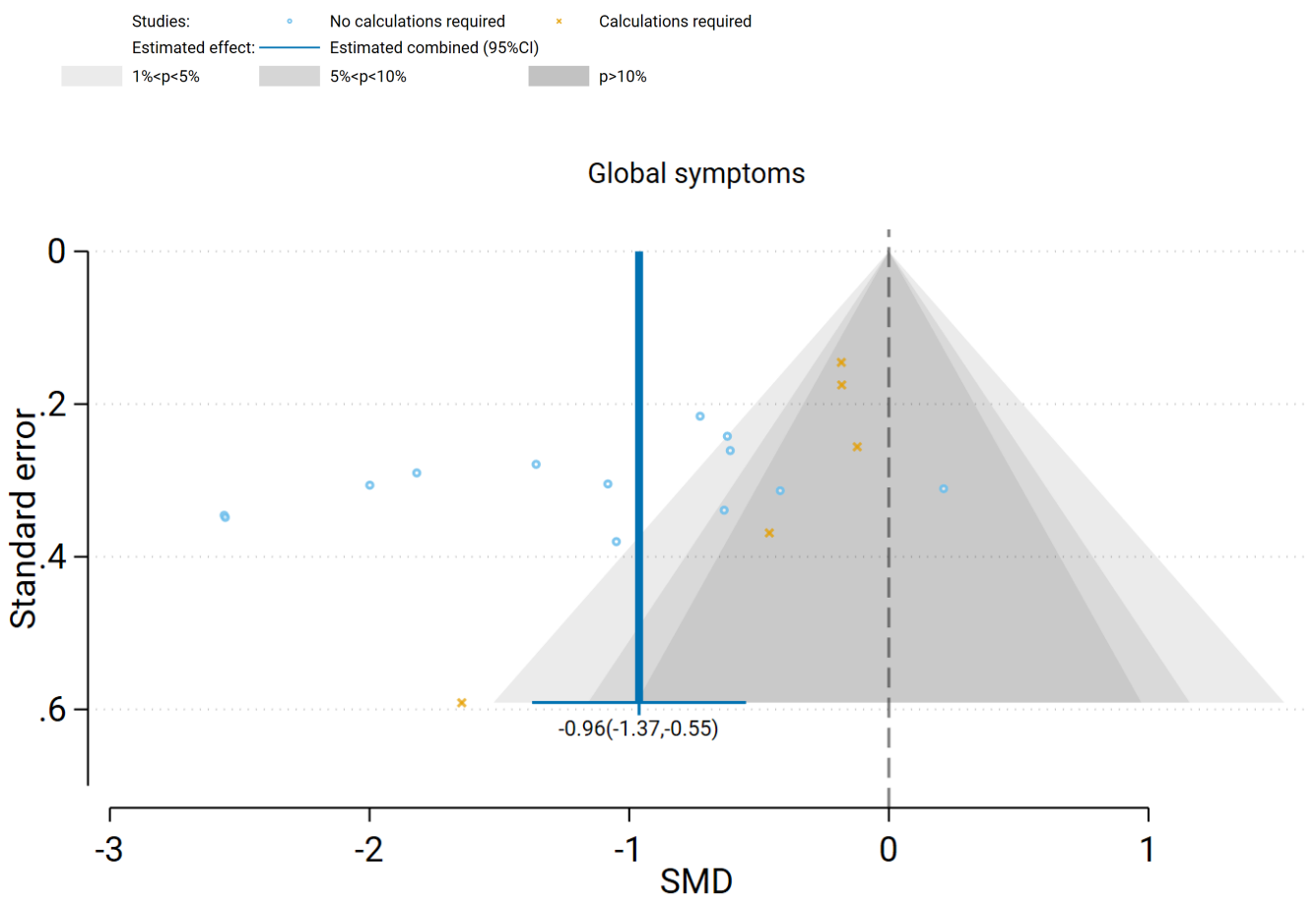


**Fig D7.1** | Contour enhanced funnel plot of estimates of SMD versus their standard errors for comparison of the effect of reflexology versus an inactive control (usual care, no intervention, sham, co-intervention given in both groups) on physical function. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

## D8 References to included studies

If multiple reports, the first citation is the index paper


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