Cochrane Australia

Systematic review of evidence on the clinical effectiveness of aromatherapy

Appendix D – additional results and citations for included studies

5 March 2024

Trusted evidence.

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Contents

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 additional subgroup analyses, sensitivity analyses, and analyses to examine the risk of bias due to missing results.

Comparison 1: Aromatherapy (any mode) versus inactive control (usual care, placebo, no intervention)

For the outcome pain, 82 studies were included in the meta-analysis for Comparison 1 which compared aromatherapy delivered by any mode to an inactive control that did not involve massage (usual care, placebo, no intervention).

Results of subgroup analyses

The following subgroup analyses were performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity).

1. Population group (both comparisons): whether the combined estimate of effect was importantly different for different population groups (surgery, procedures, chronic musculoskeletal conditions, acute musculoskeletal conditions, headache or migraine (chronic or episodic), cancer and advanced disease, labour and childbirth, other chronic pain, acute pain).
2. Mode of aromatherapy delivery (Comparison 1 only): whether the combined estimate of effect was importantly different when aromatherapy was delivered by massage compared to another mode (inhalation, topical).

Neither of the subgroup analyses provided a credible explanation for the inconsistent effects observed across studies (i.e., differences in the direction or size of the observed effect) in Comparison 1.

Population group

Results for this analysis are presented in the main report (Section 4.2, Figure 4.2.1). The test for subgroup differences was statistically significant ($P < 0.001$), however the combined estimate of effect indicated an important reduction in pain for each of the population groups except cancer and advanced disease (for which there was very low certainty evidence of little or no effect). Further, within most of the population subgroups, there was considerable variation in the effects across studies. These results suggest that population group does not provide an explanation for observed inconsistency.

Mode of aromatherapy delivery

Results for this analysis are presented in Figure D1.1. The test for subgroup differences was not statistically significant ($P = 0.453$), and the results for the two subgroups are very similar. Further, within the subgroups the effects were inconsistent across studies. As such, there is no evidence that mode of delivery explains inconsistent effects across studies.

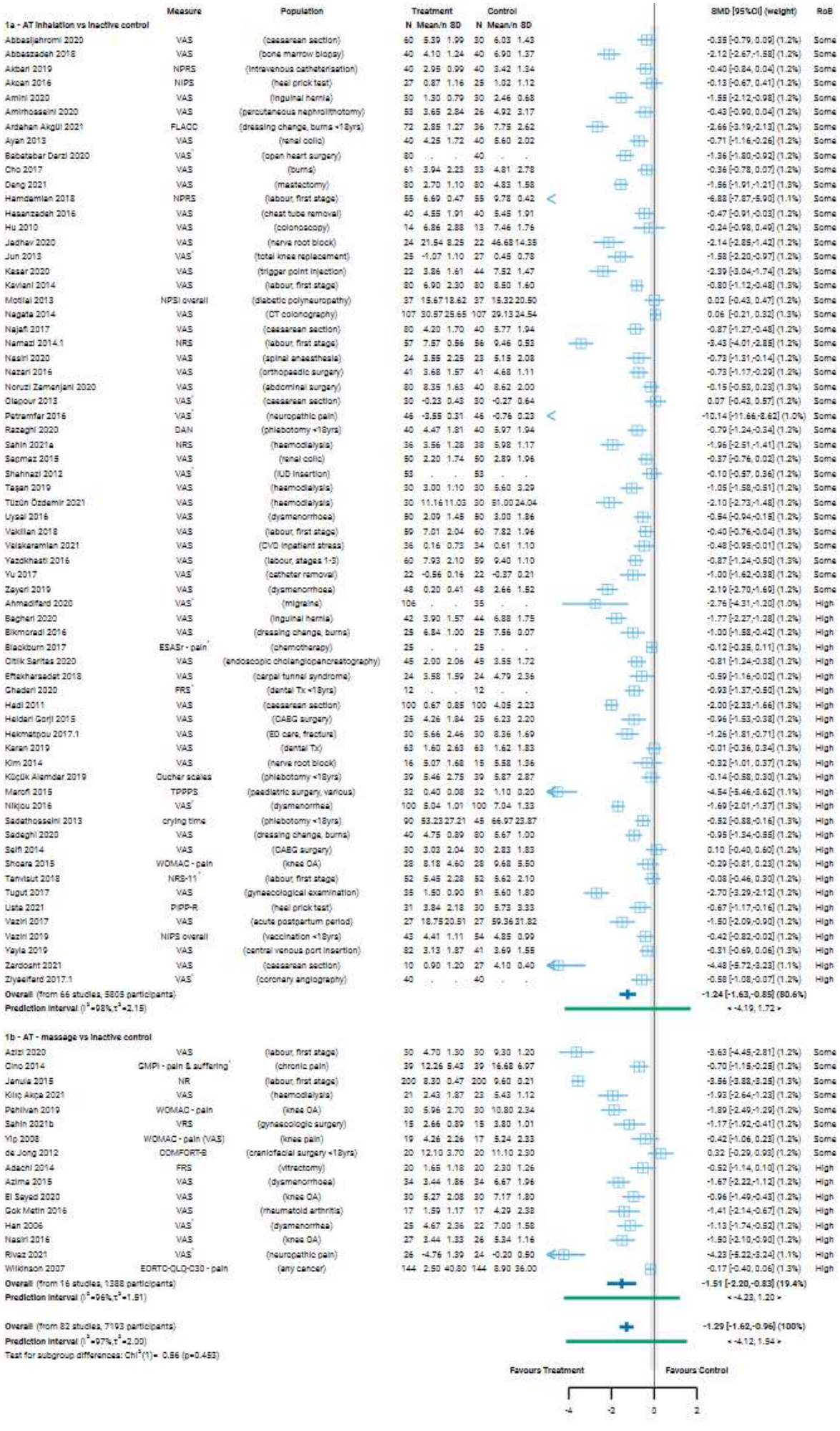
Measure
Population
Treatment
Control
N Mean/n SD
N Mean/n SD
SMD [95%CI] (weight)
RoB
1a - AT inhalation vs inactive control
Abbasijahromi 2020 VAS (caesarean section) 60 5.39 1.99 30 6.03 1.43 -0.35 [-0.79, 0.09] (1.2%) Some
Abbaszadeh 2018 VAS (bone marrow biopsy) 40 4.10 1.24 40 6.90 1.37 -2.12 [-2.67,-1.58] (1.2%) Some
Akbari 2019 NPRS (intravenous catheterisation) 40 2.95 0.99 40 3.42 1.34 -0.40 [-0.84, 0.04] (1.2%) Some
Akcan 2016 NIPS (heel prick test) 27 0.87 1.16 25 1.02 1.12 -0.13 [-0.67, 0.41] (1.2%) Some
Amini 2020 VAS (inguinal hernia) 30 1.30 0.79 30 2.46 0.68 -1.55 [-2.12,-0.98] (1.2%) Some
Amirhosseini 2020 VAS (percutaneous nephrolithotomy) 53 3.65 2.84 26 4.92 3.17 -0.43 [-0.90, 0.04] (1.2%) Some
Ardahan Akgül 2021 FLACC (dressing change, burns <18yrs) 72 2.85 1.27 36 7.75 2.62 -2.66 [-3.19,-2.13] (1.2%) Some
Ayan 2013 VAS (renal colic) 40 4.25 1.72 40 5.60 2.02 -0.71 [-1.16,-0.26] (1.2%) Some
Babatabar Darzi 2020 VAS* (open heart surgery) 80 . . 40 . . -1.36 [-1.80,-0.92] (1.2%) Some
Cho 2017 VAS (burns) 61 3.94 2.23 33 4.81 2.78 -0.36 [-0.78, 0.07] (1.2%) Some
Deng 2021 VAS (mastectomy) 80 2.70 1.10 80 4.83 1.58 -1.56 [-1.91,-1.21] (1.3%) Some
Hamdamian 2018 NPRS (labour, first stage) 55 6.69 0.47 55 9.78 0.42 -6.88 [-7.87,-5.90] (1.1%) Some
Hasanzadeh 2016 VAS (chest tube removal) 40 4.55 1.91 40 5.45 1.91 -0.47 [-0.91,-0.03] (1.2%) Some
Hu 2010 VAS (colonoscopy) 14 6.86 2.88 13 7.46 1.76 -0.24 [-0.98, 0.49] (1.2%) Some
Jadhav 2020 VAS (nerve root block) 24 21.54 8.25 22 46.68 14.35 -2.14 [-2.85,-1.42] (1.2%) Some
Jun 2013 VAS* (total knee replacement) 25 -1.07 1.10 27 0.45 0.78 -1.58 [-2.20,-0.97] (1.2%) Some
Kaser 2020 VAS (trigger point injection) 22 3.86 1.61 44 7.52 1.47 -2.39 [-3.04,-1.74] (1.2%) Some
Kavlani 2014 VAS (labour, first stage) 80 6.90 2.30 80 8.50 1.60 -0.80 [-1.12,-0.48] (1.3%) Some
Motlaf 2013 NPSI overall (diabetic polyneuropathy) 37 15.67 18.62 37 15.32 20.50 0.02 [-0.43, 0.47] (1.2%) Some
Nagata 2014 VAS (CT colonography) 107 30.57 25.65 107 29.13 24.54 0.06 [-0.21, 0.32] (1.3%) Some
Najafi 2017 VAS (caesarean section) 80 4.20 1.70 40 5.77 1.94 -0.87 [-1.27,-0.48] (1.2%) Some
Namazi 2014.1 NRS (labour, first stage) 57 7.57 0.56 56 9.46 0.53 -3.43 [-4.01,-2.85] (1.2%) Some
Nasiri 2020 VAS (spinal anaesthesia) 24 3.55 2.25 23 5.15 2.08 -0.73 [-1.31,-0.14] (1.2%) Some
Nazari 2016 VAS (orthopaedic surgery) 41 3.68 1.57 41 4.68 1.11 -0.73 [-1.17,-0.29] (1.2%) Some
Norozi Zamanjani 2020 VAS (abdominal surgery) 80 8.35 1.63 40 8.62 2.00 -0.15 [-0.53, 0.23] (1.3%) Some
Olapour 2013 VAS* (caesarean section) 30 -0.23 0.43 30 -0.27 0.64 0.07 [-0.43, 0.57] (1.2%) Some
Petramfar 2016 VAS* (neuropathic pain) 46 -3.55 0.31 46 -0.76 0.23 -10.14 [-11.66,-8.62] (1.0%) Some
Razaghi 2020 DAN (phlebotomy <18yrs) 40 4.47 1.81 40 5.97 1.94 -0.79 [-1.24,-0.34] (1.2%) Some
Sahin 2021a NRS (haemodialysis) 36 3.56 1.28 38 5.98 1.17 -1.96 [-2.51,-1.41] (1.2%) Some
Sapmaz 2015 VAS (renal colic) 50 2.20 1.74 50 2.89 1.96 -0.37 [-0.76, 0.02] (1.2%) Some
Shahnazi 2012 VAS* (IUD insertion) 53 . . 53 . . -0.10 [-0.57, 0.36] (1.2%) Some
Taşan 2019 VAS (haemodialysis) 30 3.00 1.10 30 5.60 3.29 -1.05 [-1.58,-0.51] (1.2%) Some
Tüzün Özdemir 2021 VAS (haemodialysis) 30 11.16 11.03 30 51.00 24.04 -2.10 [-2.73,-1.48] (1.2%) Some
Uysal 2016 VAS (dysmenorrhoea) 50 2.09 1.45 50 3.00 1.86 -0.54 [-0.94,-0.15] (1.2%) Some
Vakilian 2018 VAS (labour, first stage) 59 7.01 2.04 60 7.82 1.96 -0.40 [-0.76,-0.04] (1.3%) Some
Valsakarmian 2021 VAS (CVD inpatient stress) 36 0.16 0.73 34 0.61 1.10 -0.48 [-0.95,-0.01] (1.2%) Some
Yazdkhasti 2016 VAS (labour, stages 1-3) 60 7.93 2.10 59 9.40 1.10 -0.87 [-1.24,-0.50] (1.3%) Some
Yu 2017 VAS* (catheter removal) 22 -0.56 0.16 22 -0.37 0.21 -1.00 [-1.62,-0.38] (1.2%) Some
Zeyari 2019 VAS (dysmenorrhoea) 48 0.20 0.41 48 2.66 1.52 -2.19 [-2.70,-1.69] (1.2%) Some
Ahmadifard 2020 VAS* (migraine) 106 . . 35 . . -2.76 [-4.31,-1.20] (1.0%) High
Bagheri 2020 VAS (inguinal hernia) 42 3.90 1.57 44 6.88 1.75 -1.77 [-2.27,-1.28] (1.2%) High
Bikmoradi 2016 VAS (dressing change, burns) 25 6.84 1.00 25 7.56 0.07 -1.00 [-1.58,-0.42] (1.2%) High
Blackburn 2017 ESASr - pain* (chemotherapy) 25 . . 25 . . -0.12 [-0.35, 0.11] (1.3%) High
Ciftik Saritas 2020 VAS (endoscopic cholangiopancreatography) 45 2.00 2.06 45 3.55 1.72 -0.81 [-1.24,-0.38] (1.2%) High
Effakharsadat 2018 VAS (carpal tunnal syndrome) 24 3.58 1.59 24 4.79 2.36 -0.59 [-1.16,-0.02] (1.2%) High
Ghaderi 2020 FRS* (dental Tx <18yrs) 12 . . 12 . . -0.93 [-1.37,-0.50] (1.2%) High
Hadi 2011 VAS (caesarean section) 100 0.67 0.85 100 4.05 2.23 -2.00 [-2.33,-1.66] (1.3%) High
Heidari Gorji 2015 VAS (CABG surgery) 25 4.26 1.84 25 6.23 2.20 -0.96 [-1.53,-0.38] (1.2%) High
Hekmatpou 2017.1 VAS (ED care, fracture) 30 5.66 2.46 30 8.36 1.69 -1.26 [-1.81,-0.71] (1.2%) High
Karan 2019 VAS (dental Tx) 63 1.60 2.63 63 1.62 1.83 -0.01 [-0.36, 0.34] (1.3%) High
Kim 2014 VAS (nerve root block) 16 5.07 1.68 15 5.58 1.36 -0.32 [-1.01, 0.37] (1.2%) High
Küçük Alemdar 2019 Ouchar scales (phlebotomy <18yrs) 39 5.46 2.75 39 5.87 2.87 -0.14 [-0.58, 0.30] (1.2%) High
Marofi 2015 TPPPS (paediatric surgery, various) 32 0.40 0.08 32 1.10 0.20 -4.54 [-5.46,-3.62] (1.1%) High
Nikjou 2016 VAS* (dysmenorrhea) 100 5.04 1.01 100 7.04 1.33 -1.69 [-2.01,-1.37] (1.3%) High
Sadathosseini 2013 crying time (phlebotomy <18yrs) 90 53.23 27.21 45 66.97 23.87 -0.52 [-0.88,-0.16] (1.3%) High
Sadeghi 2020 VAS (dressing change, burns) 40 4.75 0.89 80 5.67 1.00 -0.95 [-1.34,-0.55] (1.2%) High
Saifi 2014 VAS (CABG surgery) 30 3.03 2.04 30 2.83 1.83 0.10 [-0.40, 0.60] (1.2%) High
Shoara 2015 WOMAC - pain (knee OA) 28 8.18 4.60 28 9.68 5.50 -0.29 [-0.81, 0.23] (1.2%) High
Tanvisut 2018 NRS-11* (labour, first stage) 52 5.46 2.28 52 5.62 2.10 -0.08 [-0.46, 0.30] (1.2%) High
Tugut 2017 VAS (gynaecological examination) 35 1.50 0.90 51 5.60 1.80 -2.70 [-3.29,-2.12] (1.2%) High
Usta 2021 PIPP-R (heel prick test) 31 3.84 2.18 30 5.73 3.33 -0.67 [-1.17,-0.16] (1.2%) High
Vazirі 2017 VAS (acute postpartum period) 27 18.75 20.51 27 59.36 31.82 -1.50 [-2.09,-0.90] (1.2%) High
Vazirі 2019 NIPS overall (vaccination <18yrs) 43 4.41 1.11 54 4.85 0.99 -0.42 [-0.82,-0.02] (1.2%) High
Yayla 2019 VAS (central venous port insertion) 82 3.13 1.87 41 3.69 1.55 -0.31 [-0.69, 0.06] (1.3%) High
Zardosht 2021 VAS (caesarean section) 10 0.90 1.20 27 4.10 0.40 -4.48 [-5.72,-3.23] (1.1%) High
Ziyaeifard 2017.1 VAS* (coronary angiography) 40 . . 40 . . -0.58 [-1.08,-0.07] (1.2%) High
Overall (from 66 studies, 5805 participants) -1.24 [-1.63,-0.85] (80.6%)
Prediction interval (I^2=98%,τ^2=2.15) < -4.19, 1.72 >
1b - AT - massage vs inactive control
Azizi 2020 VAS (labour, first stage) 30 4.70 1.30 30 9.30 1.20 -3.63 [-4.45,-2.81] (1.2%) Some
Cino 2014 GMPI - pain & suffering* (chronic pain) 39 12.26 5.43 39 16.68 6.97 -0.70 [-1.15,-0.25] (1.2%) Some
Janula 2015 NR (labour, first stage) 200 8.30 0.47 200 9.60 0.21 -3.56 [-3.88,-3.25] (1.3%) Some
Kılıç Akça 2021 VAS (haemodialysis) 21 2.43 1.87 23 5.43 1.12 -1.93 [-2.64,-1.23] (1.2%) Some
Pehlivan 2019 WOMAC - pain (knee OA) 30 5.96 2.70 30 10.80 2.34 -1.89 [-2.49,-1.29] (1.2%) Some
Sahin 2021b VRS (gynaecologic surgery) 15 2.66 0.89 15 3.80 1.01 -1.17 [-1.92,-0.41] (1.2%) Some
Yip 2008 WOMAC - pain (VAS) (knee pain) 19 4.26 2.26 17 5.24 2.33 -0.42 [-1.06, 0.23] (1.2%) Some
de Jong 2012 COMFORT-B (craniofacial surgery <18yrs) 20 12.10 3.70 20 11.10 2.50 0.32 [-0.29, 0.93] (1.2%) Some
Adachi 2014 FRS (vitrectomy) 20 1.65 1.18 20 2.30 1.26 -0.52 [-1.14, 0.10] (1.2%) High
Azima 2015 VAS (dysmenorrhoea) 34 3.44 1.86 34 6.67 1.96 -1.67 [-2.22,-1.12] (1.2%) High
El Sayad 2020 VAS (knee OA) 30 5.27 2.08 30 7.17 1.80 -0.96 [-1.49,-0.43] (1.2%) High
Gok Metin 2016 VAS (rheumatoid arthritis) 17 1.59 1.17 17 4.29 2.38 -1.41 [-2.14,-0.67] (1.2%) High
Han 2006 VAS* (dysmenorrhea) 25 4.67 2.36 22 7.00 1.58 -1.13 [-1.74,-0.52] (1.2%) High
Nasiri 2016 VAS (knee OA) 27 3.44 1.33 26 5.34 1.16 -1.50 [-2.10,-0.90] (1.2%) High
Rivaz 2021 VAS* (neuropathic pain) 26 -4.76 1.39 24 -0.20 0.50 -4.23 [-5.22,-3.24] (1.1%) High
Wilkinson 2007 EORTC-QLQ-C30 - pain (any cancer) 144 2.50 40.80 144 8.90 36.00 -0.17 [-0.40, 0.06] (1.3%) High
Overall (from 16 studies, 1388 participants) -1.51 [-2.20,-0.83] (19.4%)
Prediction interval (I^2=96%,τ^2=1.51) < -4.23, 1.20 >
Overall (from 82 studies, 7193 participants) -1.29 [-1.62,-0.96] (100%)
Prediction interval (I^2=97%,τ^2=2.00) < -4.12, 1.54 >
Test for subgroup differences: $Chi^2(1)$= 0.56 (p=0.453)
Favours Treatment
Favours Control
-4
-2
0
2

Fig D1.1 | Forest plot for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on pain; subgrouped by mode of aromatherapy delivery. SMD = standardised mean difference. Blue lines show 95% confidence intervals (CI) and green lines show prediction intervals (PI). The shaded grey area indicates the pre-specified range where the effect of aromatherapy is considered to be no different from control (SMD -0.2 to 0.2 standard units). ^ indicates studies for which data transformation or imputation was required to include the result in the meta-analysis. This included crossover trials and studies that reported results as a dichotomous or ordinal outcome (identifiable because no mean or SD is reported for the study in the forest plot).

Results of sensitivity analyses

Table D1.1 presents results for the original analysis (all studies, random effects model) and three 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
    a. transforming or imputing statistics, or
    b. 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 or imputing statistics was necessary, and then also removing studies for which change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Table D1.1. Sensitivity analyses for pain outcome, both comparisons

Comparison[1]	Sensitivity analysis	Purpose of sensitivity analysis	No trials	Original effect (95% CI)	No trials	Sensitivity analysis effect
C1. AT (any mode) v inactive control (not massage)	No imputation or transformations[2]	Investigate robustness of MA effect	82	SMD -1.29 (-1.62 to -0.96); I2 = 97%	73	SMD -1.33 (-1.70 to -0.96); I2 = 97%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			67	SMD -1.21 (-1.52 to -0.91); I2 = 96%
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			82	SMD -0.91 (-0.96 to -0.86); I2 = 95%
C2. AT (massage) v control (massage)	No imputation or transformations[2]	Investigate robustness of MA effect	19	SMD -0.72 (-1.19 to -0.25); I2 = 93%	15	SMD -0.71 (-1.13 to -0.11); I2 = 92%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			13	SMD -0.56 (-1.05 to 0.07); I2 = 86%
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			19	SMD -0.66 (-0.77 to -0.55); I2 = 89%

[1] C1. includes studies that compare AT (any mode, massage or not) to an inactive control that does not involve massage; C2. includes studies that compare AT (massage) to a massage control that is comparable to that used to deliver AT.

[2] This analysis was limited to trials that reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals

[3] 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. AT = aromatherapy; MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

Bias due to missing results from the meta-analysis

For Comparison 1 the combined effect estimated from the fixed effect model (SMD -0.89) was smaller than from the random effects model (SMD -1.29) (Table 4.1.1), but in both cases the effect estimate indicated a reduction in pain greater than the threshold for an important effect (Table D1.1). The contour-enhanced funnel plot in Figure D1.2 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).

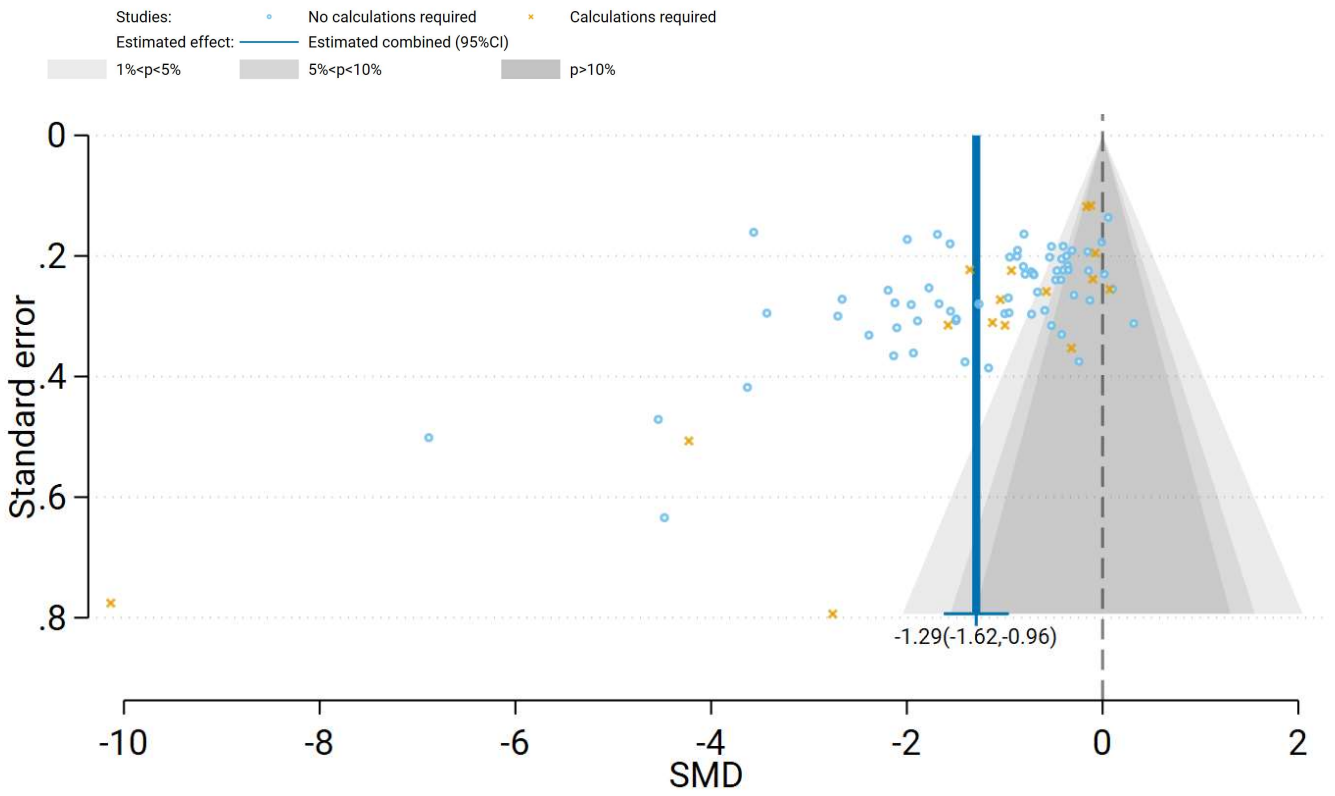

Fig D1.2 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on pain. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

Comparison 2: Aromatherapy (massage) versus inactive control (massage)

For the outcome pain, 19 studies were included in the meta-analysis for Comparison 2 which compared aromatherapy delivered by massage to an inactive massage control (i.e. a comparable form of massage to that received by the intervention group).

Results of subgroup analyses

Population group

A single subgroup analysis was performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity). Specifically, whether the combined estimate of effect was importantly different for the different population groups contributing to the analysis (chronic musculoskeletal conditions, surgery, procedures, labour and childbirth, other chronic pain, other acute pain).

The subgroup analysis did not provide a credible explanation for the inconsistent effects observed across studies (i.e., differences in the direction or size of the observed effect) in Comparison 2. Results for this analysis are presented in the main report (Section 4.2, Figure 4.2.2). The test for subgroup differences was significant ($P < 0.001$), however within most of the population subgroups, there was considerable variation in the effects across studies. These results suggest that population group does not fully explain the observed inconsistency.

Results of sensitivity analyses

Table D1.1 presents results for the original analysis (all studies, random effects model) and three sensitivity analyses for Comparison 2. The combined estimate of effect was similar in the original analysis and the sensitivity analyses removing studies for which transforming or imputing statistics was necessary, and when we removed any additional

studies for which change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Bias due to missing results from the meta-analysis

The combined effect estimated from the fixed effect model (SMD -0.66) was similar to that from the random effects model (SMD -0.72) (Table D1.1); in both cases the effect estimate indicated a reduction in pain greater than the threshold for an important effect (Table D1.1). The contour-enhanced funnel plot in Figure D1.3 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).

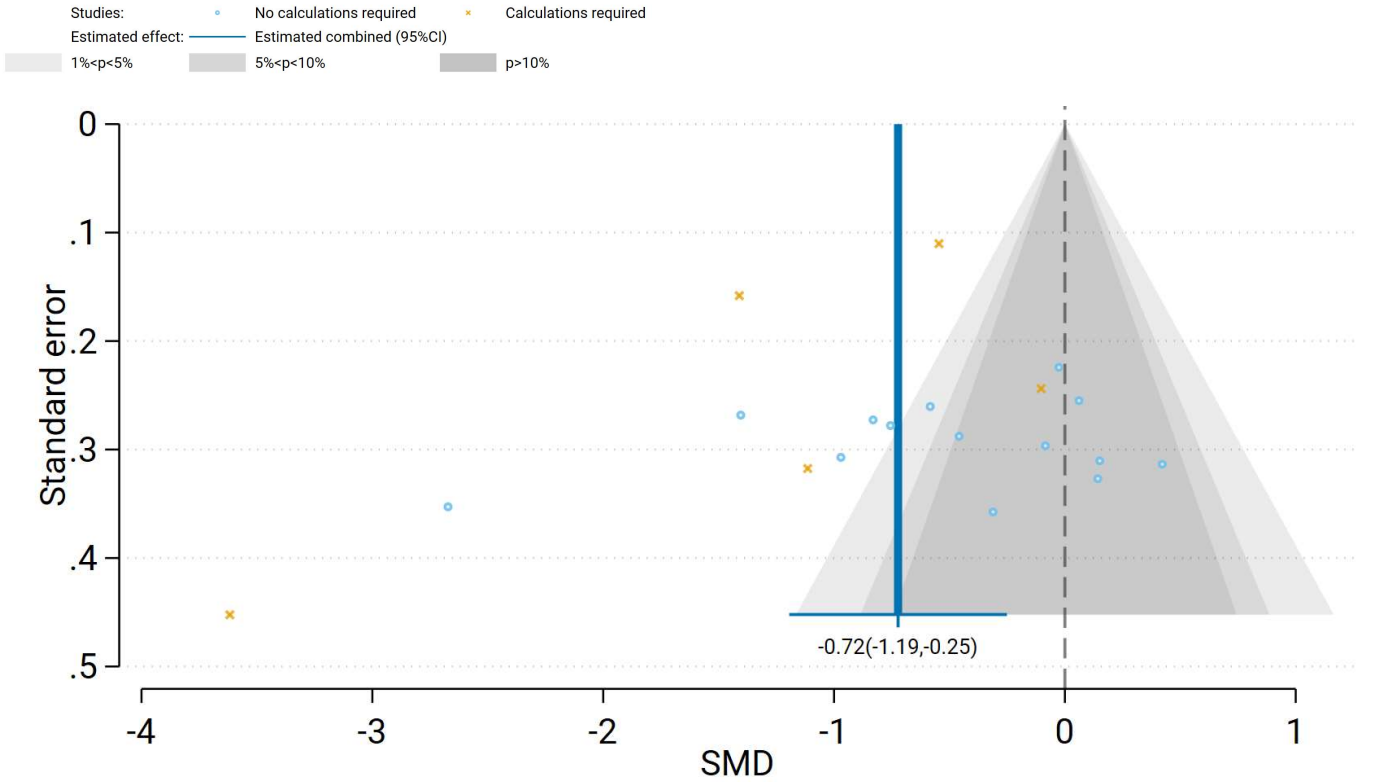

Fig D1.3 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 2. the effect of aromatherapy (massage) versus inactive control (massage) on pain. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

D2 Nausea and vomiting

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

For the outcome nausea and vomiting, all 23 studies that could be included in a meta-analysis compared aromatherapy (any mode) to an inactive control (usual care, placebo, no intervention) that did not involve massage.

No studies compared aromatherapy delivered by massage to massage alone, and so results are only for comparison 1.

Comparison 1: Aromatherapy (any mode) versus inactive control (usual care, placebo, no intervention)

Results of subgroup analyses

The following subgroup analyses were performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity).

1. Population group: whether the combined estimate of effect was importantly different for different population groups (cancer and advanced disease, surgery, procedures, pregnancy).

2. Mode of aromatherapy delivery: whether the combined estimate of effect was importantly different when aromatherapy was delivered by massage compared to another mode (inhalation, topical).

Neither of the subgroup analyses provided a credible explanation for the inconsistent effects observed across studies (i.e., differences in the direction or size of the observed effect) in comparison 1.

Population group

Results for this analysis are presented in the main report (Section 4.3, Figure 4.3.1). The test for subgroup differences was not statistically significant (P = 0.525) and the combined estimate of effect indicated an important reduction in nausea and vomiting for each of the population groups except procedures. The single study among people undergoing a procedure showed little or no effect on nausea and vomiting, but this single study has little weight in the analysis and as such this does not provide an explanation for observed inconsistency.

Mode of aromatherapy delivery

Results for this analysis are presented in Figure D2.1. The test for subgroup differences was significant (P = 0.007), however the confidence intervals for the two subgroups are entirely overlapping (indicating compatible results) and only two of the 23 studies contributed to the subgroup in which aromatherapy was delivered by massage (as opposed to inhalation or topically). Further, within the subgroup in which aromatherapy was delivered by inhalation or topically, the effects were inconsistent across studies. As such, no conclusions can be drawn about whether effects are different depending on mode of delivery.

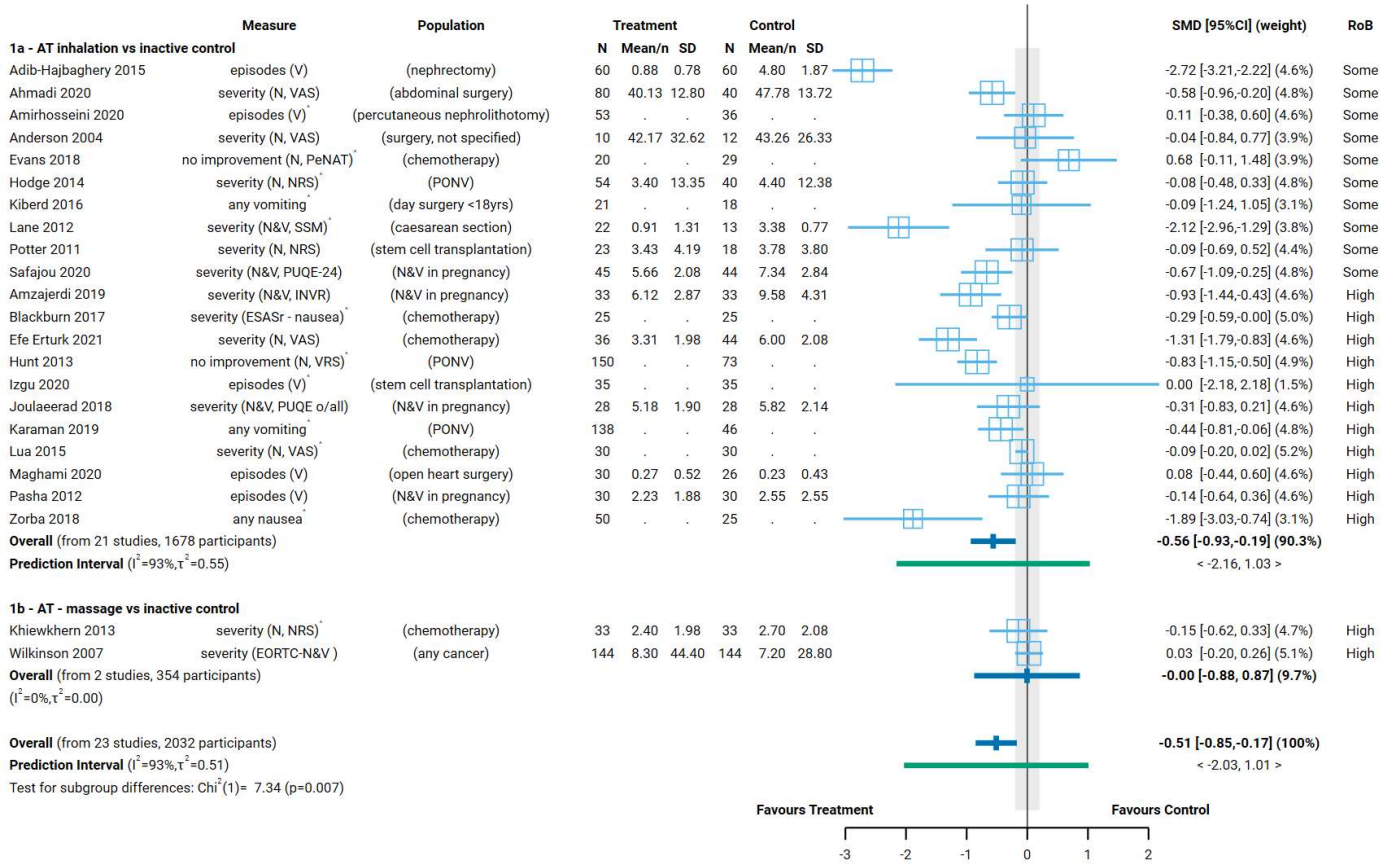

Fig D2.1 | Forest plot for comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on nausea and vomiting; subgrouped by mode of aromatherapy delivery. Measures: N = nausea, V = vomiting, N&V = nausea and vomiting. SMD = standardised mean difference. Blue lines show 95% confidence intervals (CI) and green lines show prediction intervals (PI). The shaded grey area indicates the pre-specified range where the effect of aromatherapy is considered to be no different from control (SMD -0.2 to 0.2 standard units). ^ indicates studies for which data transformation or imputation was required to include the result in the meta-analysis. This included crossover trials and studies that reported results as a dichotomous or ordinal outcome (identifiable because no mean or SD is reported for the study in the forest plot).

Results of sensitivity analyses

Table D2.1 presents results for the original analysis (all studies, random effects model) and three 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
    a. transforming or imputing statistics, or
    b. 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 analysis removing studies for which transforming or imputing statistics was necessary, indicating that the result was robust to these assumptions required to include these results. For the nausea and vomiting outcome, the second sensitivity analysis (1b) was not required because post-intervention values and their standard deviations were available for all studies.

Table D2.1. Sensitivity analyses for nausea and vomiting outcome, both comparisons

Comparison[1]	Sensitivity analysis	Purpose of sensitivity analysis	No trials	Original effect (95% CI)	No trials	Sensitivity analysis effect
C1. AT (any mode) v inactive control (not massage)	No imputation or transformations[2]	Investigate robustness of MA effect	23	SMD -0.51 (-0.81 to -0.17); I2 = 93%	11	SMD -0.61 (-1.17 to -0.06); I2 = 92%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			11	As above (no additional studies removed)
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			23	SMD -0.29 (-0.36 to -0.22); I2 = 89%
C2. AT (massage) v control (massage)	No imputation or transformations[2]	Investigate robustness of MA effect	0	No studies contributed to this comparison for this outcome.		
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect				
	Fixed effect analysis	Investigate small study effects (bias due to missing results)				

[1] C1. includes studies that compare AT (any mode, massage or not) to an inactive control that does not involve massage; C2 includes studies that compare AT (massage) to a massage control that is comparable to that used to deliver AT.

[2] This analysis was limited to trials that reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals

[3] 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. AT = aromatherapy; 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 -0.29) was smaller than from the random effects model (SMD -0.51) (Table D2.1), but the difference was minimal and both indicated a reduction in nausea and vomiting greater than the threshold for an important effect. The exception was for studies among people undergoing chemotherapy for cancer, where the combined effect estimated from the fixed effect model (SMD -0.13) suggested little or no difference in nausea and vomiting with aromatherapy whereas the random effects model showed an important reduction (SMD -0.35). The contour-enhanced funnel plot in Figure D2.2 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).

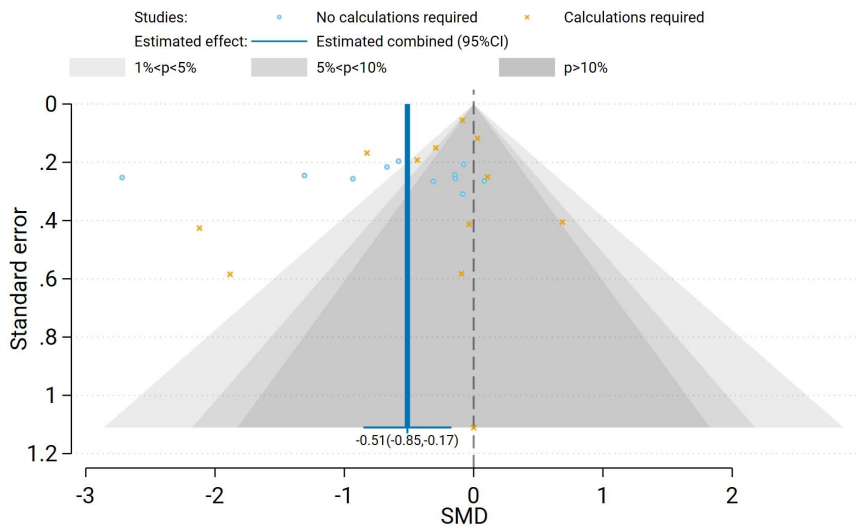

Fig D2.2 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on nausea and vomiting. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

D3 Sleep

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

For the outcome sleep, all 22 studies that could be included in a meta-analysis compared aromatherapy (any mode) to an inactive control (usual care, placebo, no intervention) that did not involve massage.

No studies compared aromatherapy delivered by massage to massage alone (Comparison 2).

Comparison 1: Aromatherapy (any mode) versus inactive control (usual care, placebo, no intervention)

Results of subgroup analyses

The following subgroup analyses were performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity).

1. Population group: whether the combined estimate of effect was importantly different for different population groups (cancer and advanced disease, surgery, hospitalisation, chronic insomnia, sleep disturbance).
2. Mode of aromatherapy delivery: whether the combined estimate of effect was importantly different when aromatherapy was delivered by massage compared to another mode (inhalation, topical).

Neither of the subgroup analyses provided a credible explanation for the inconsistent effects observed across studies (i.e., differences in the direction or size of the observed effect) in Comparison 1. While there are differences in the size of the estimated intervention effect across studies for this comparison and outcome, the effect estimate for all 22 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.

Population group

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 = 0.4) and 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).

Mode of aromatherapy delivery

Results for this analysis are presented in Figure D3.1. The test for subgroup differences was not statistically significant (P = 0.646) and the effect estimate for each of the two subgroups was similar. Further, within the subgroups, the effects were inconsistent across studies. As such, no conclusions can be drawn about whether effects are different depending on mode of delivery, although all studies show important benefit.

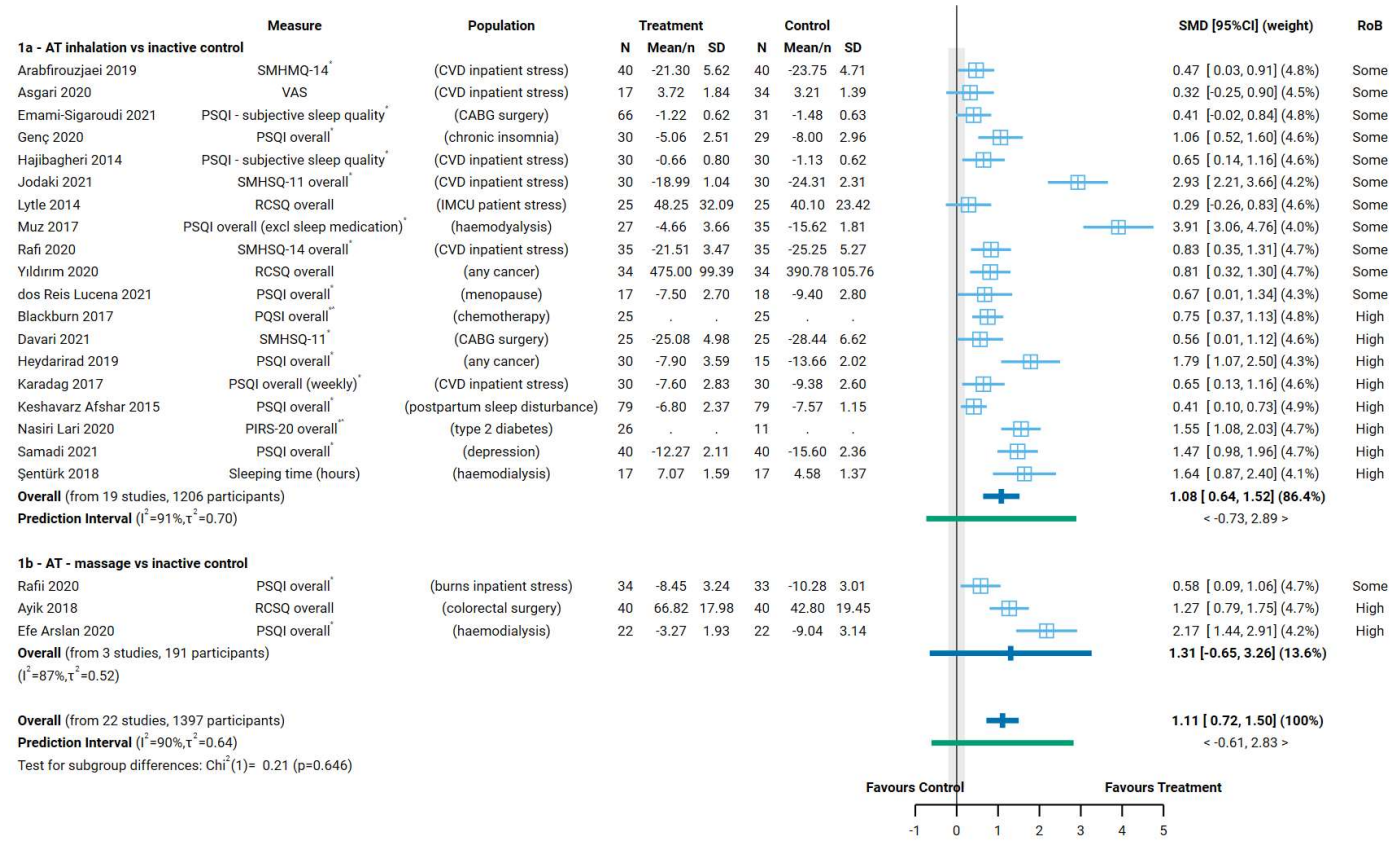

Fig D3.1 | Forest plot for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on sleep; subgrouped by mode of aromatherapy delivery. SMD = standardised mean difference. Blue lines show 95% confidence intervals (CI) and green lines show prediction intervals (PI). The shaded grey area indicates the pre-specified range where the effect of aromatherapy is considered to be no different from control (SMD -0.2 to 0.2 standard units). ^ indicates studies for which data transformation or imputation was required to include the result in the meta-analysis. This included crossover trials and studies that reported results as a dichotomous or ordinal outcome (identifiable because no mean or SD is reported for the study in the forest plot).

Results of sensitivity analyses

Table D3.1 presents results for the original analysis (all studies, random effects model) and three 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
    a. transforming or imputing statistics, or
    b. 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 analysis removing studies for which transforming or imputing statistics was necessary, indicating that the result was robust to these assumptions

required to include these results. For the sleep quality outcome, the second sensitivity analysis (1b) was not required because post-intervention values and their standard deviations were available for all studies.

Table D3.1. Sensitivity analyses for sleep quality outcome, both comparisons

Comparison[1]	Sensitivity analysis	Purpose of sensitivity analysis	No trials	Original effect (95% CI)	No trials	Sensitivity analysis effect
C1. AT (any mode) v inactive control (not massage)	No imputation or transformations[2]	Investigate robustness of MA effect	22	SMD 1.11 (0.72 to 1.50); I^2 = 90%	20	SMD 1.11 (0.68 to 1.54); I^2 = 91%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			20	As above (no additional studies removed)
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			22	SMD 0.91 (0.80 to 1.014); I^2 = 86%
C2. AT (massage) v control (massage)	No imputation or transformations[2]	Investigate robustness of MA effect	0	No studies contributed to this comparison for this outcome.		
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect				
	Fixed effect analysis	Investigate small study effects (bias due to missing results)				

[1] C1. includes studies that compare AT (any mode, massage or not) to an inactive control that does not involve massage; C2 includes studies that compare AT (massage) to a massage control that is comparable to that used to deliver AT.

[2] This analysis was limited to trials that reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals

[3] 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. AT = aromatherapy; 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 0.91) was smaller than from the random effects model (SMD 1.11) (Table D3.1), but both indicated an improvement in sleep quality greater than the threshold for an important effect. The contour-enhanced funnel plot in Figure D3.2 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).

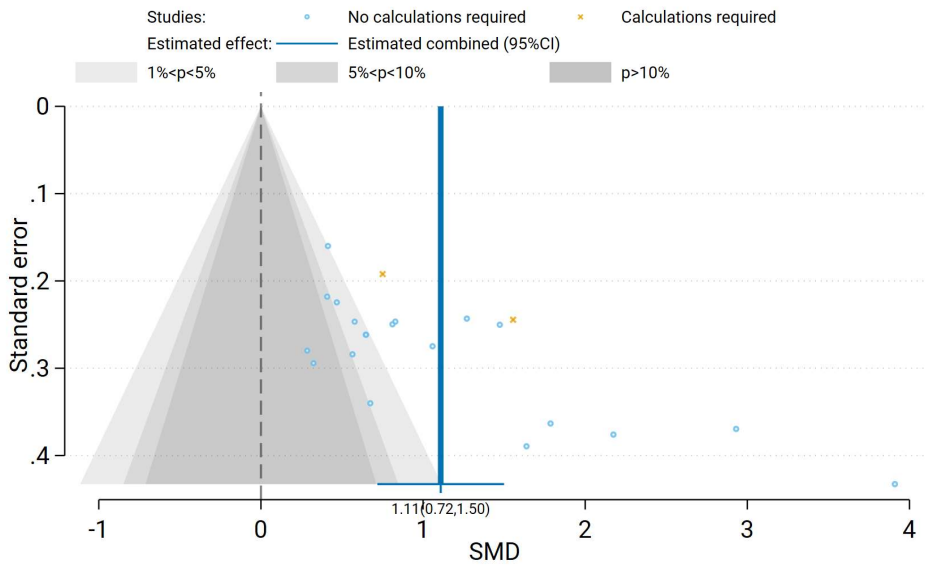

Fig D3.2 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on sleep quality. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

D4 Fatigue

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

Comparison 1: Aromatherapy (any mode) versus inactive control (usual care, placebo, no intervention)

For the outcome fatigue, 18 studies were included in the meta-analysis for Comparison 1 which compared aromatherapy delivered by any mode to an inactive control that did not involve massage (usual care, placebo, no intervention).

Results of subgroup analyses

The following subgroup analyses were performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity).

1. Population group (both comparisons): whether the combined estimate of effect was importantly different for different population groups (chronic musculoskeletal conditions, cancer and advanced disease, pregnancy, other chronic conditions).
2. Mode of aromatherapy delivery (Comparison 1 only): whether the combined estimate of effect was importantly different when aromatherapy was delivered by massage compared to another mode (inhalation, topical).

Neither of the subgroup analyses provided a credible explanation for the inconsistent effects observed across studies (i.e., differences in the direction or size of the observed effect) in Comparison 1.

Population group

Results for this analysis are presented in the main report (Section 4.5, Figure 4.5.1). The test for subgroup differences was statistically significant (P < 0.007) however, within most of the population subgroups, there was considerable variation in the effects across studies. These results suggest that population group does not provide an explanation for observed inconsistency.

Mode of aromatherapy delivery

Results for this analysis are presented in Figure D4.1. The test for subgroup differences was not statistically significant (P = 0.939), and the results for the two subgroups are very similar. Further, within the subgroups the effects were

inconsistent across studies. As such, there is no evidence that mode of delivery explains inconsistent effects across studies.

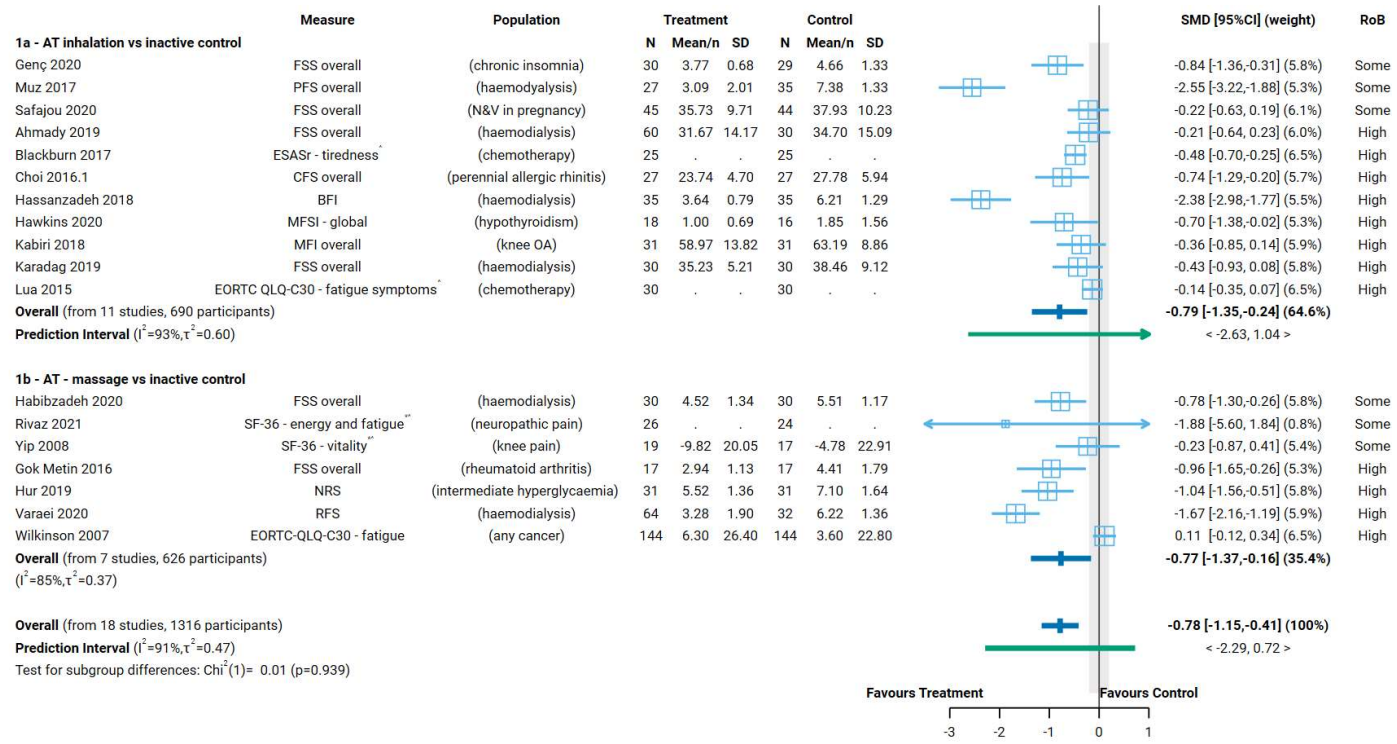

Fig D4.1 | Forest plot for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on fatigue; subgrouped by mode of aromatherapy delivery. SMD = standardised mean difference. Blue lines show 95% confidence intervals (CI) and green lines show prediction intervals (PI). The shaded grey area indicates the pre-specified range where the effect of aromatherapy is considered to be no different from control (SMD -0.2 to 0.2 standard units). ^ indicates studies for which data transformation or imputation was required to include the result in the meta-analysis. This included crossover trials and studies that reported results as a dichotomous or ordinal outcome (identifiable because no mean or SD is reported for the study in the forest plot).

Results of sensitivity analyses

Table D4.1 presents results for the original analysis (all studies, random effects model) and three 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
    a. transforming or imputing statistics, or
    b. 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 or imputing statistics was necessary, and then also removing studies for which change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Table D4.1. Sensitivity analyses for fatigue outcome, both comparisons

Comparison[1]	Sensitivity analysis	Purpose of sensitivity analysis	No trials	Original effect (95% CI)	No trials	Sensitivity analysis effect
C1. AT (any mode) v inactive control (not massage)	No imputation or transformations[2]	Investigate robustness of MA effect	18	SMD -0.78 (-1.15 to -0.41); I2 = 91%	15	SMD -0.85 (-1.28 to -0.42); I2 = 90%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			14	SMD -0.89 (-1.34 to -0.44); I2 = 90%
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			18	SMD -0.47 (-0.56 to -0.37); I2 = 88%
C2. AT (massage) v control (massage)	No imputation or transformations[2]	Investigate robustness of MA effect	4	SMD -0.38 (-0.93 to 0.17); I2 = 30%	3	SMD -0.36 (-1.14 to -0.41); I2 = 40%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			2	SMD -0.35 (-4.08 to 3.38); I2 = 68%
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			4	SMD -0.39 (-0.68 to -0.11); I2 = 23%

[1] C1. includes studies that compare AT (any mode, massage or not) to an inactive control that does not involve massage; C2 includes studies that compare AT (massage) to a massage control that is comparable to that used to deliver AT.

[2] This analysis was limited to trials that reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals

[3] 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. AT = aromatherapy; MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

Bias due to missing results from the meta-analysis

For Comparison 1, the combined effect estimated from the fixed effect model (SMD -0.47) was smaller than from the random effects model (SMD -0.78) (Table D4.1), but in both cases the effect estimate indicated a reduction in fatigue greater than the threshold for an important effect (Table D4.1). The contour-enhanced funnel plot in Figure D4.2 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).

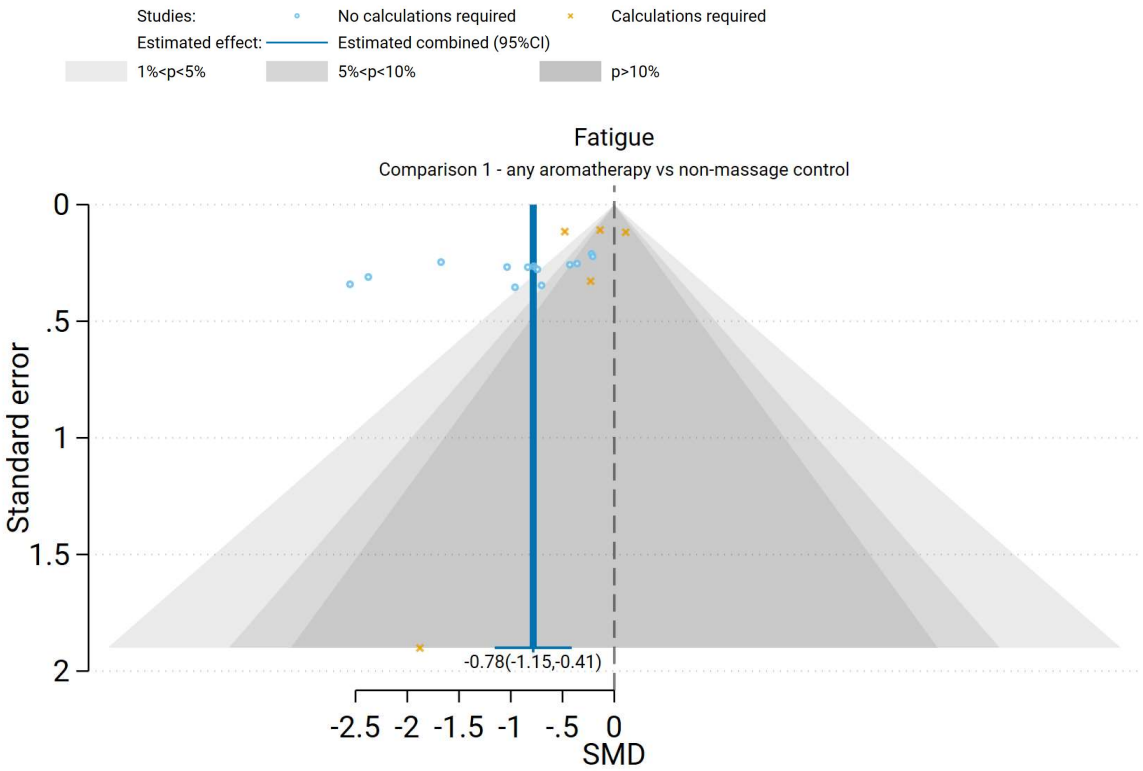

Fig D4.2 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on fatigue. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

Comparison 2: Aromatherapy (massage) versus inactive control (massage)

For the outcome fatigue, 4 studies were included in the meta-analysis for Comparison 2 which compared aromatherapy delivered by massage to an inactive massage control (i.e. a comparable form of massage to that received by the intervention group).

Results of subgroup analyses

Population group

No subgroup analyses were performed as all studies were among people with chronic conditions. There was no important inconsistency in the results across studies in this subgroup; confidence intervals overlapped, and the heterogeneity statistics indicated that any inconsistency might not be important (I^2 = 30%).

Results of sensitivity analyses

Table D4.1 presents results for the original analysis (all studies, random effects model) and three sensitivity analyses for Comparison 2. The combined estimate of effect was similar in the original analysis and the sensitivity analyses removing studies for which transforming or imputing statistics was necessary, and when we removed any additional studies for which change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Bias due to missing results from the meta-analysis

The combined effect estimated from the fixed effect model (SMD -0.38) was similar to that from the random effects model (SMD -0.39) (Table D4.1). The contour-enhanced funnel plot in Figure D4.3 includes too few studies to provide any evidence about missing results (publication bias).

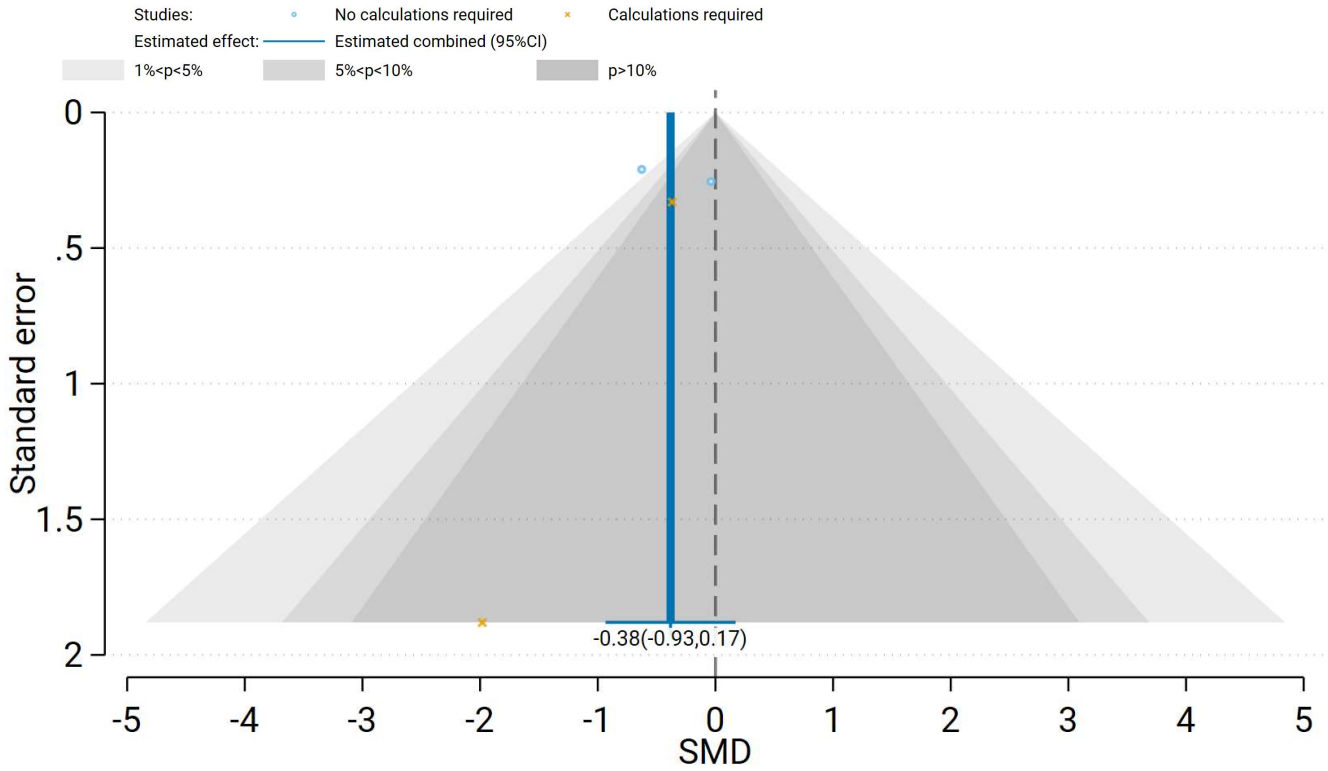

Fig D4.3 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 2. the effect of aromatherapy (massage) versus inactive control (massage) on fatigue. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

D5 Emotional functioning and mental health

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

Comparison 1: Aromatherapy (any mode) versus inactive control (usual care, placebo, no intervention)

For the outcome emotional functioning and mental health, 86 studies were included in the meta-analysis for Comparison 1 which compared aromatherapy delivered by any mode to an inactive control that did not involve massage (usual care, placebo, no intervention).

Results of subgroup analyses

The following subgroup analyses were performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity).

1. Population group (both comparisons): whether the combined estimate of effect was importantly different for different population groups (surgery, procedures, cancer and advanced disease, hospitalisation, labour and childbirth, dementia, mental distress).
2. Mode of aromatherapy delivery (Comparison 1 only): whether the combined estimate of effect was importantly different when aromatherapy was delivered by massage compared to another mode (inhalation, topical).

Neither of the subgroup analyses provided a credible explanation for the inconsistent effects observed across studies (i.e., differences in the direction or size of the observed effect) in Comparison 1.

Population group

Results for this analysis are presented in the main report (Section 4.6, Figure 4.6.1). The test for subgroup differences was statistically significant ($P < 0.001$), however the combined estimate of effect indicated an important reduction in emotional functioning and mental health in the majority of the population groups, the I^2 remained high in most of the population subgroups, and there was considerable variation in the effects across studies within the two largest

subgroups (surgery and procedures which contribute 50/86 studies). These results suggest that population group does not provide an explanation for observed inconsistency.

Mode of aromatherapy delivery

Results for this analysis are presented in Figure D5.1. The test for subgroup differences was not statistically significant (P = 0.434), the results for the two subgroups are similar, both indicating an important improvement in emotional functioning and mental health (SMD -0.93 for inhalation subgroup; SMD -0.69 for massage subgroup). Further, within the subgroups the effects were inconsistent across studies. As such, this analysis does not provide evidence that mode of delivery explains inconsistent effects across studies.

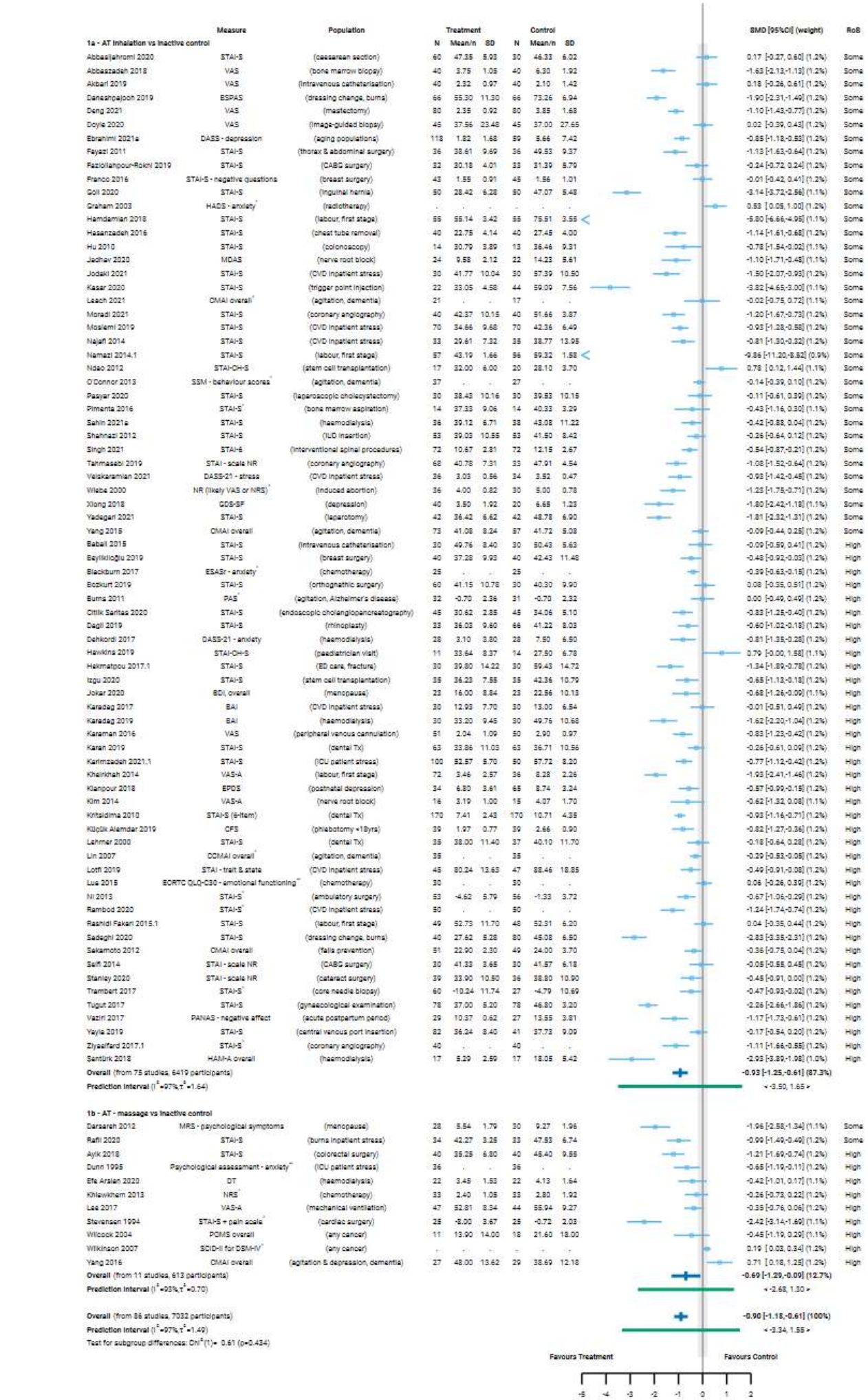
Measure
Population
Treatment
Control
N
Mean/n
SD
SMD [95%CI] (weight)
RoB
1a - AT Inhalation vs Inactive control
Abbasijahromi 2020 STAI-S (caesarean section) 60 47.35 5.93 30 46.33 6.02 0.17 [-0.27, 0.60] (1.2%) Some
Abbaszadeh 2018 VAS (bone marrow biopsy) 40 3.75 1.05 40 6.30 1.92 -1.63 [-2.13,-1.13] (1.2%) Some
Akbari 2019 VAS (Intravenous catheterisation) 40 2.32 0.97 40 2.10 1.42 0.18 [-0.26, 0.61] (1.2%) Some
Daneshpajooh 2019 BSPAS (dressing change, burns) 66 55.30 11.30 66 73.26 6.94 -1.90 [-2.31,-1.49] (1.2%) Some
Deng 2021 VAS (mastectomy) 80 2.35 0.92 80 3.85 1.68 -1.10 [-1.43,-0.77] (1.2%) Some
Doyle 2020 VAS (Image-guided biopsy) 45 37.56 23.48 45 37.00 27.65 0.02 [-0.39, 0.43] (1.2%) Some
Ebrahimi 2021a DASS - depression (aging populations) 118 1.82 1.68 59 5.66 7.42 -0.85 [-1.18,-0.53] (1.2%) Some
Fayazi 2011 STAI-S (thorax & abdominal surgery) 36 38.61 9.69 36 49.53 9.37 -1.13 [-1.63,-0.64] (1.2%) Some
Fazlollahpour-Rokni 2019 STAI-S (CABG surgery) 32 30.18 4.01 33 31.39 5.79 -0.24 [-0.72, 0.24] (1.2%) Some
Franco 2016 STAI-S - negative questions (breast surgery) 43 1.55 0.91 45 1.56 1.01 -0.01 [-0.42, 0.41] (1.2%) Some
Goli 2020 STAI-S (Inguinal hernia) 50 28.42 6.28 50 47.07 5.48 -3.14 [-3.72,-2.56] (1.1%) Some
Graham 2003 HADS - anxiety* (radiotherapy) . . . . . . 0.53 [0.05, 1.00] (1.2%) Some
Hamdamian 2018 STAI-S (labour, first stage) 55 55.14 3.42 55 75.51 3.55 -5.80 [-6.66,-4.95] (1.1%) Some
Hasanzadeh 2016 STAI-S (chest tube removal) 40 22.75 4.14 40 27.45 4.00 -1.14 [-1.61,-0.68] (1.2%) Some
Hu 2010 STAI-S (colonoscopy) 14 30.79 3.89 13 36.46 9.31 -0.78 [-1.54,-0.02] (1.1%) Some
Jadhav 2020 MDAS (nerve root block) 24 9.58 2.12 22 14.23 5.61 -1.10 [-1.71,-0.48] (1.1%) Some
Jodaki 2021 STAI-S (CVD inpatient stress) 30 41.77 10.04 30 57.39 10.50 -1.50 [-2.07,-0.93] (1.2%) Some
Kasar 2020 STAI-S (trigger point injection) 22 33.05 4.58 44 59.09 7.56 -3.82 [-4.65,-3.00] (1.1%) Some
Lasch 2021 CMAI overall* (agitation, dementia) 21 . . 17 . . -0.02 [-0.75, 0.72] (1.1%) Some
Moradi 2021 STAI-S (coronary angiography) 40 42.37 10.15 40 51.66 3.87 -1.20 [-1.67,-0.73] (1.2%) Some
Moslemi 2019 STAI-S (CVD inpatient stress) 70 34.66 9.68 70 42.36 6.49 -0.93 [-1.28,-0.58] (1.2%) Some
Najafi 2014 STAI-S (CVD inpatient stress) 33 29.61 7.32 35 38.77 13.95 -0.81 [-1.30,-0.32] (1.2%) Some
Namazi 2014.1 STAI-S (labour, first stage) 97 43.19 1.66 96 59.32 1.58 -9.86 [-11.20,-8.52] (0.9%) Some
Ndao 2012 STAI-OH-S (stem cell transplantation) 17 32.00 6.00 20 28.10 3.70 0.78 [0.12, 1.44] (1.1%) Some
O'Connor 2013 SSM - behaviour scores* (agitation, dementia) 37 . . 27 . . -0.14 [-0.39, 0.10] (1.2%) Some
Pasyar 2020 STAI-S (laparoscopic cholecystectomy) 30 38.43 10.16 30 39.53 10.15 -0.11 [-0.61, 0.39] (1.2%) Some
Pimenta 2016 STAI-S* (bone marrow aspiration) 14 37.33 9.06 14 40.33 3.29 -0.43 [-1.16, 0.30] (1.1%) Some
Sahin 2021a STAI-S (haemodialysis) 36 39.12 6.71 38 43.08 11.22 -0.42 [-0.88, 0.04] (1.2%) Some
Shahnazi 2012 STAI-S (ILID insertion) 53 39.03 10.55 53 41.50 8.42 -0.26 [-0.64, 0.12] (1.2%) Some
Singh 2021 STAI-6 (Interventional spinal procedures) 72 10.67 2.81 72 12.15 2.67 -0.54 [-0.87,-0.21] (1.2%) Some
Tahmasebi 2019 STAI - scale NR (coronary angiography) 68 40.78 7.31 33 47.91 4.54 -1.08 [-1.52,-0.64] (1.2%) Some
Velakaramian 2021 DASS-21 - stress (CVD inpatient stress) 36 3.03 0.56 34 3.52 0.47 -0.93 [-1.42,-0.45] (1.2%) Some
Wiebe 2000 NR (likely VAS or NRS)* (Induced abortion) 36 4.00 0.82 30 5.00 0.78 -1.23 [-1.75,-0.71] (1.2%) Some
Xiong 2018 GDS-SF (depression) 40 3.50 1.92 20 6.65 1.23 -1.80 [-2.42,-1.18] (1.1%) Some
Yadegari 2021 STAI-S (laparotomy) 42 36.42 5.62 42 48.78 6.90 -1.81 [-2.32,-1.31] (1.2%) Some
Yang 2015 CMAI overall (agitation, dementia) 73 41.08 8.24 57 41.72 5.08 -0.09 [-0.44, 0.25] (1.2%) Some
Babali 2015 STAI-S (Intravenous catheterisation) 30 49.76 8.40 30 50.43 5.63 -0.09 [-0.59, 0.41] (1.2%) High
Beyliklioglu 2019 STAI-S (breast surgery) 40 37.28 9.93 40 42.43 11.48 -0.48 [-0.92,-0.03] (1.2%) High
Blackburn 2017 ESASr - anxiety* (chemotherapy) 25 . . 25 . . -0.39 [-0.63,-0.15] (1.2%) High
Bozkurt 2019 STAI-S (orthognathic surgery) 60 41.15 10.78 30 40.30 9.90 0.08 [-0.35, 0.51] (1.2%) High
Burns 2011 PAS* (agitation, Alzheimer's disease) 32 -0.70 2.39 31 -0.70 2.32 0.00 [-0.49, 0.49] (1.2%) High
Citlik Saritas 2020 STAI-S (endoscopic cholangiopancreatography) 45 30.62 2.85 45 34.06 5.10 -0.83 [-1.25,-0.40] (1.2%) High
Degli 2019 STAI-S (rhinoplasty) 33 36.03 9.60 66 41.22 8.03 -0.60 [-1.02,-0.18] (1.2%) High
Dehkordi 2017 DASS-21 - anxiety (haemodialysis) 28 3.10 3.80 28 7.50 6.50 -0.81 [-1.35,-0.28] (1.2%) High
Hawkins 2019 STAI-OH-S (paediatrician visit) 11 33.64 8.37 14 27.50 6.78 0.79 [-0.00, 1.58] (1.1%) High
Hekmatpou 2017.1 STAI-S (ED care, fracture) 30 39.80 14.22 30 59.43 14.72 -1.34 [-1.89,-0.78] (1.2%) High
Izgu 2020 STAI-S (stem cell transplantation) 35 36.23 7.55 35 42.36 10.79 -0.65 [-1.13,-0.18] (1.2%) High
Jokar 2020 BDI, overall (menopause) 23 16.00 8.84 23 22.96 10.13 -0.68 [-1.26,-0.09] (1.1%) High
Karadag 2017 BAI (DVD inpatient stress) 30 12.93 7.70 30 13.00 6.54 -0.01 [-0.51, 0.49] (1.2%) High
Karadag 2019 BAI (haemodialysis) 30 33.20 9.45 30 49.76 10.68 -1.62 [-2.20,-1.04] (1.2%) High
Karaman 2016 VAS (peripheral venous cannulation) 51 2.04 1.09 50 2.90 0.97 -0.83 [-1.23,-0.42] (1.2%) High
Karan 2019 STAI-S (dental Tx) 63 33.86 11.03 63 36.71 10.56 -0.26 [-0.61, 0.09] (1.2%) High
Karimzadeh 2021.1 STAI-S (ICU patient stress) 100 52.57 5.70 50 57.72 8.20 -0.77 [-1.12,-0.42] (1.2%) High
Khairkhah 2014 VAS-A (labour, first stage) 72 3.46 2.57 36 6.28 2.26 -1.93 [-2.41,-1.46] (1.2%) High
Kianpour 2018 EPDS (postnatal depression) 34 6.80 3.61 65 8.74 3.24 -0.57 [-0.99,-0.15] (1.2%) High
Kim 2014 VAS-A (nerve root block) 16 3.19 1.00 15 4.07 1.70 -0.62 [-1.32, 0.08] (1.1%) High
Kritsidima 2010 STAI-S (6-item) (dental Tx) 170 7.41 2.43 170 10.71 4.35 -0.93 [-1.16,-0.71] (1.2%) High
Küçük Alemdar 2019 CFS (phlebotomy <18yrs) 39 1.97 0.77 39 2.66 0.90 -0.82 [-1.27,-0.36] (1.2%) High
Lehmer 2000 STAI-S (dental Tx) 35 38.00 11.40 37 40.10 11.70 -0.18 [-0.64, 0.28] (1.2%) High
Lin 2007 CCMAI overall* (agitation, dementia) 35 . . 35 . . -0.29 [-0.83,-0.05] (1.2%) High
Lotfi 2019 STAI - trait & state (DVD inpatient stress) 45 80.24 13.63 47 88.46 18.85 -0.49 [-0.91,-0.08] (1.2%) High
Lua 2015 EORTC QLQ-C30 - emotional functioning** (chemotherapy) 30 . . 30 . . 0.06 [-0.26, 0.39] (1.2%) High
Ni 2013 STAI-S* (ambulatory surgery) 53 -4.62 5.79 56 -1.33 3.72 -0.67 [-1.06,-0.29] (1.2%) High
Rambod 2020 STAI-S* (DVD inpatient stress) 50 . . 50 . . -1.24 [-1.74,-0.74] (1.2%) High
Rashidi Fakari 2015.1 STAI-S (labour, first stage) 49 52.73 11.70 48 52.31 6.20 0.04 [-0.35, 0.44] (1.2%) High
Sadeghi 2020 STAI-S (dressing change, burns) 40 27.62 5.28 80 45.08 6.50 -2.83 [-3.35,-2.31] (1.2%) High
Sakamoto 2012 CMAI overall (falls prevention) 51 22.90 2.30 49 24.00 3.70 -0.36 [-0.75, 0.04] (1.2%) High
Seifi 2014 STAI - scale NR (CABG surgery) 30 41.33 3.65 30 41.57 6.18 -0.05 [-0.55, 0.45] (1.2%) High
Stanley 2020 STAI - scale NR (cataract surgery) 39 33.90 10.50 36 38.80 10.90 -0.46 [-0.91, 0.00] (1.2%) High
Trambert 2017 STAI-S* (core needle biopsy) 60 -10.24 11.74 27 -4.79 10.69 -0.47 [-0.93,-0.02] (1.2%) High
Tugut 2017 STAI-S (gynaecological examination) 78 37.00 5.20 78 46.80 3.20 -2.26 [-2.66,-1.86] (1.2%) High
Vaziri 2017 PANAS - negative affect (acute postpartum period) 29 10.37 0.62 27 13.55 3.81 -1.17 [-1.73,-0.61] (1.2%) High
Yayla 2019 STAI-S (central venous port insertion) 82 36.24 8.40 41 37.73 9.09 -0.17 [-0.54, 0.20] (1.2%) High
Ziyaelfard 2017.1 STAI-S* (coronary angiography) 40 . . 40 . . -1.11 [-1.66,-0.55] (1.2%) High
Semtürk 2018 HAM-A overall (haemodialysis) 17 5.29 2.59 17 18.06 5.42 -2.93 [-3.89,-1.98] (1.0%) High
Overall (from 75 studies, 6419 participants) -0.93 [-1.25,-0.61] (87.3%)
Prediction Interval (I^2 =97%, τ^2 =1.64) < -3.50, 1.65 >
1b - AT - massage vs Inactive control
Darsareh 2012 MRS - psychological symptoms (menopause) 28 5.54 1.79 30 9.27 1.96 -1.96 [-2.58,-1.34] (1.1%) Some
Rafii 2020 STAI-S (burns inpatient stress) 34 42.27 3.25 33 47.53 6.74 -0.99 [-1.49,-0.49] (1.2%) Some
Aylik 2018 STAI-S (colorectal surgery) 40 35.25 6.80 40 45.40 9.55 -1.21 [-1.69,-0.74] (1.2%) High
Dunn 1995 Psychological assessment - anxiety** (ICU patient stress) 36 . . 36 . . -0.65 [-1.19,-0.11] (1.2%) High
Efe Arslan 2020 DT (haemodialysis) 22 3.45 1.53 22 4.13 1.64 -0.42 [-1.01, 0.17] (1.1%) High
Khiewkhern 2013 NRS* (chemotherapy) 33 2.40 1.05 33 2.80 1.92 -0.26 [-0.73, 0.22] (1.2%) High
Lee 2017 VAS-A (mechanical ventilation) 47 52.81 8.34 44 55.94 9.27 -0.35 [-0.76, 0.06] (1.2%) High
Stevenson 1994 STAI-S + pain scale* (cardiac surgery) 25 -8.00 3.67 25 -0.72 2.03 -2.42 [-3.14,-1.69] (1.1%) High
Wilcock 2004 POMS overall (any cancer) 11 13.90 14.00 18 21.60 18.00 -0.45 [-1.19, 0.29] (1.1%) High
Wilkinson 2007 SCID-II for DSM-IV* (any cancer) . . . . . . 0.19 [0.03, 0.34] (1.2%) High
Yang 2016 CMAI overall (agitation & depression, dementia) 27 48.00 13.62 29 38.69 12.18 0.71 [0.18, 1.25] (1.2%) High
Overall (from 11 studies, 613 participants) -0.69 [-1.29,-0.09] (12.7%)
Prediction Interval (I^2 =93%, τ^2 =0.70) < -2.68, 1.30 >
Overall (from 86 studies, 7032 participants) -0.90 [-1.18,-0.61] (100%)
Prediction Interval (I^2 =97%, τ^2 =1.49) < -3.34, 1.55 >
Test for subgroup differences: Chi^2(1)= 0.61 (p=0.434)
Favours Treatment
Favours Control
-5 -4 -3 -2 -1 0 1 2

Fig D5.1 | Forest plot for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on emotional functioning and mental health; subgrouped by mode of aromatherapy delivery. SMD = standardised mean difference. Blue lines show 95% confidence intervals (CI) and green lines show prediction intervals (PI). The shaded grey area indicates the pre-specified range where the effect of aromatherapy is considered to be no different from control (SMD -0.2 to 0.2 standard units). ^ indicates studies for which data transformation or imputation was required to include the result in the meta-analysis. This included crossover trials and studies that reported results as a dichotomous or ordinal outcome (identifiable because no mean or SD is reported for the study in the forest plot).

Results of sensitivity analyses

Table D5.1 presents results for the original analysis (all studies, random effects model) and three 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
    a. transforming or imputing statistics, or
    b. 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 or imputing statistics was necessary, and then also removing studies for which change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Table D5.1. Sensitivity analyses for emotional functioning and mental health outcome, both comparisons

Comparison[1]	Sensitivity analysis	Purpose of sensitivity analysis	No trials	Original effect (95% CI)	No trials	Sensitivity analysis effect
C1. AT (any mode) v inactive control (not massage)	No imputation or transformations[2]	Investigate robustness of MA effect	86	SMD -0.90 (-1.18 to -0.61); I2 = 97%	70	SMD -1.00 (-1.34 to -0.66); I2 = 97%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			69	SMD -1.00 (-1.35 to -0.66); I2 = 97%
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			86	SMD -0.61 (-0.65 to -0.56); I2 = 93%
C2. AT (massage) v control (massage)	No imputation or transformations[2]	Investigate robustness of MA effect	11	SMD -0.22 (-0.59 to 0.14); I2 = 93%	8	SMD -0.25 (-0.77 to 0.27); I2 = 83%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			8	As above (no additional studies removed)
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			11	SMD -0.25 (-0.40 to -0.09); I2 = 73%

[1] C1. includes studies that compare AT (any mode, massage or not) to an inactive control that does not involve massage; C2 includes studies that compare AT (massage) to a massage control that is comparable to that used to deliver AT.

[2] This analysis was limited to trials that reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals

[3] 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. AT = aromatherapy; MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

Bias due to missing results from the meta-analysis

For Comparison 1, the combined effect estimated from the fixed effect model (SMD -0.61) was smaller than from the random effects model (SMD -0.90) (Table D5.1), but in both cases the effect estimate indicated an improvement in emotional functioning and mental health greater than the threshold for an important effect (Table D5.1). The contour-enhanced funnel plot in Figure D5.2 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).

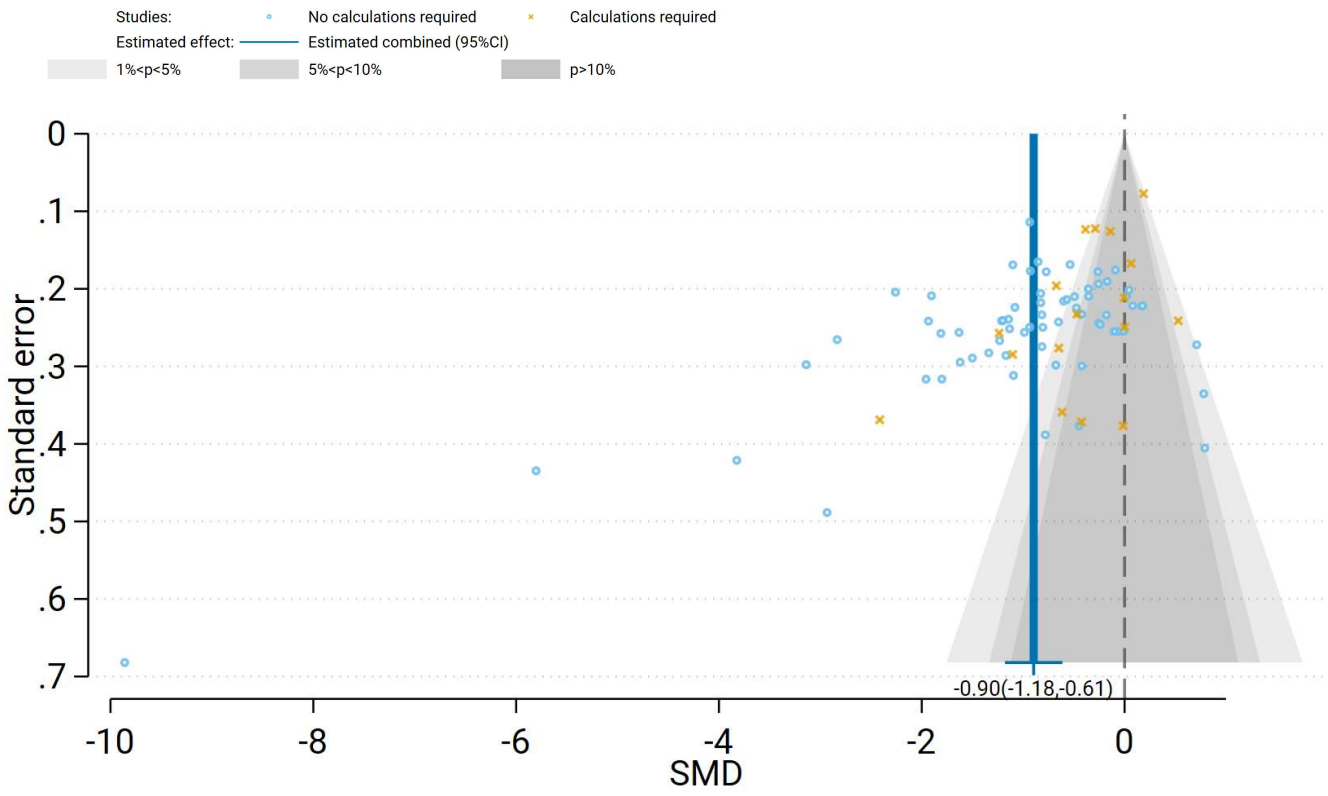

Fig D5.2 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on emotional functioning and mental health. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

Comparison 2: Aromatherapy (massage) versus inactive control (massage)

For the outcome emotional functioning and mental health, 11 studies were included in the meta-analysis for Comparison 2 which compared aromatherapy delivered by massage to an inactive massage control (i.e. a comparable form of massage to that received by the intervention group).

Results of subgroup analyses

Population group

A single subgroup analysis was performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity). Specifically, whether the combined estimate of effect was importantly different for the different population groups contributing to the analysis (cancer and advanced disease, surgery, hospitalisation, dementia, mental distress).

Results for this analysis are presented in the main report (Section 4.6, Figure 4.6.2). The test for subgroup differences was statistically significant (P < 0.001) and remaining inconsistency within each subgroup was not serious. While the subgroup analysis may partly explain inconsistent results in the overall analysis for Comparison 2 (i.e., differences in the direction or size of the observed effect across studies), there are too few studies in each subgroup to be sure.

Results of sensitivity analyses

Table D5.1 presents results for the original analysis (all studies, random effects model) and two sensitivity analyses for Comparison 2. The combined estimate of effect was similar in the original analysis and the sensitivity analysis removing

studies for which transforming or imputing statistics was necessary. No studies were included for which change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Bias due to missing results from the meta-analysis

The combined effect estimated from the fixed effect model (SMD -0.22) was similar to that from the random effects model (SMD -0.25) (Table D5.1). The contour-enhanced funnel plot in Figure D5.3 includes too few studies to draw any conclusions about missing studies.

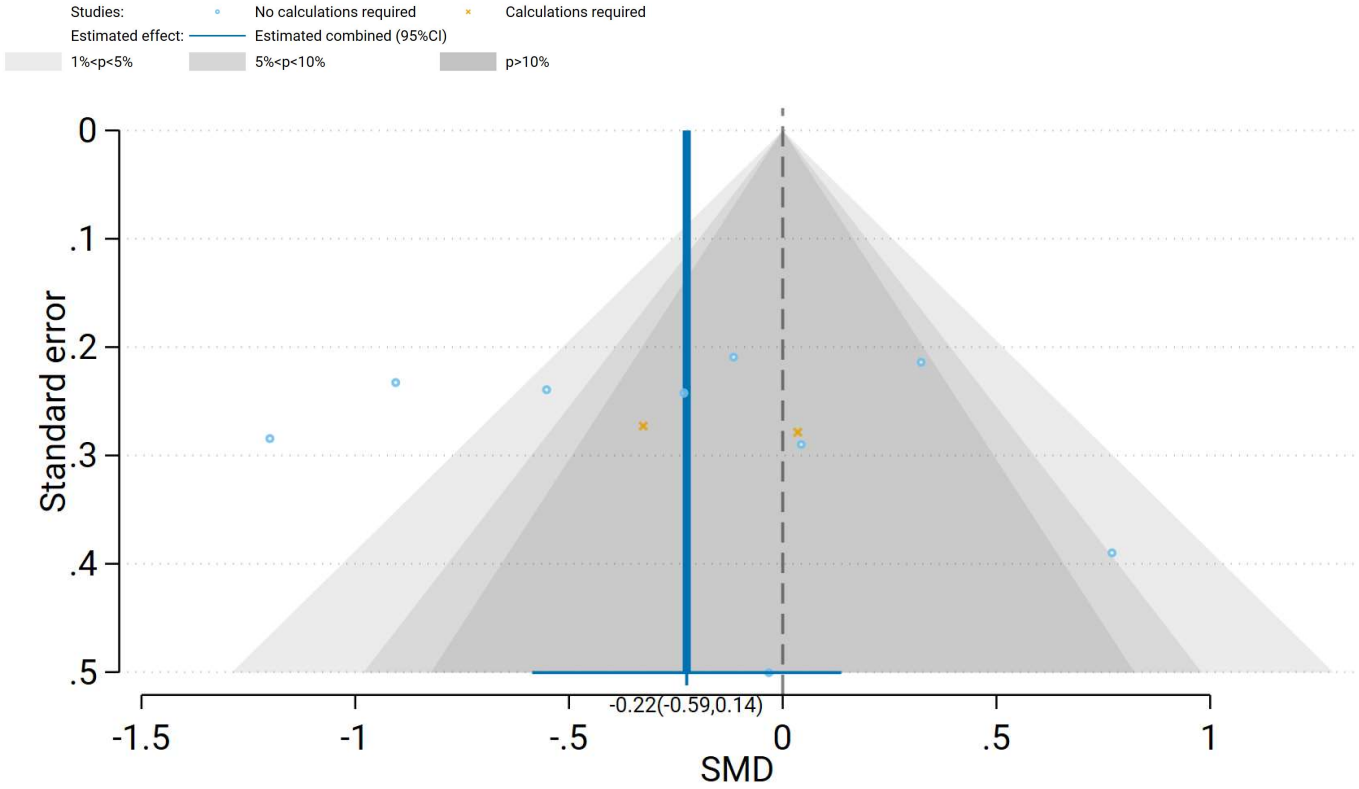

Fig D5.3 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 2. the effect of aromatherapy (massage) versus inactive control (massage) on emotional functioning and mental health. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

D6 Health-related quality of life (HR-QoL)

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

Comparison 1: Aromatherapy (any mode) versus inactive control (usual care, placebo, no intervention)

For the outcome health-related quality of life (HR-QoL), 14 studies were included in the meta-analysis for Comparison 1 which compared aromatherapy delivered by any mode to an inactive control that did not involve massage (usual care, placebo, no intervention).

Results of subgroup analyses

The following subgroup analyses were performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity).

1. Population group (both comparisons): whether the combined estimate of effect was importantly different for different population groups (cancer and advanced disease, chronic conditions).
2. Mode of aromatherapy delivery (Comparison 1 only): whether the combined estimate of effect was importantly different when aromatherapy was delivered by massage compared to another mode (inhalation, topical).

Neither of the subgroup analyses provided a credible explanation for the inconsistent effects observed across studies (i.e., differences in the direction or size of the observed effect) in Comparison 1. While there are differences in the size of the estimated intervention effect across studies for this comparison and outcome, the confidence intervals overlap for almost all studies (suggesting compatible results) and the effect estimate for most studies is above the threshold for an important improvement in HR-QoL (i.e. an SMD > 0.2). As such, the observed inconsistency is considered unimportant as it is does not alter the interpretation of findings for this outcome

Population group

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 < 0.489) and within the two population subgroups, there was considerable variation in the size of effect across studies. These results suggest that population group does not provide an explanation for any observed inconsistency in the overall analysis. Overall, there is evidence that the effects are consistent across population groups (all showing important benefit, despite variation in the magnitude of benefit).

Mode of aromatherapy delivery

Results for this analysis are presented in Figure D6.1. The test for subgroup differences was not statistically significant (P = 0.436), and the point estimate for both subgroups indicates important improvement in HR-QoL with aromatherapy. Results were consistent when aromatherapy was delivered by inhalation/topically (overlapping confidence intervals, I^2 = 0%), but inconsistent in the massage subgroup suggesting mode of delivery does not fully explain any inconsistent effects in the overall analysis.

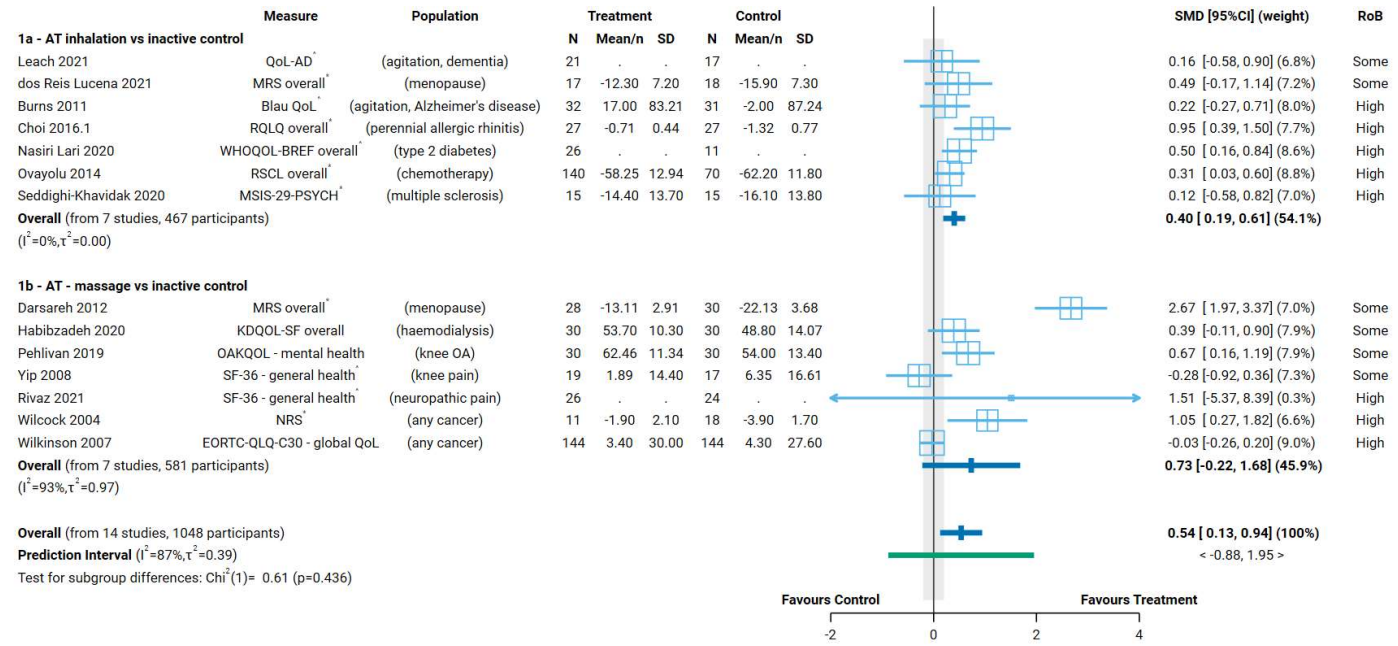

Fig D6.1 | Forest plot for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on HR-QoL; subgrouped by mode of aromatherapy delivery. SMD = standardised mean difference. Blue lines show 95% confidence intervals (CI) and green lines show prediction intervals (PI). The shaded grey area indicates the pre-specified range where the effect of aromatherapy is considered to be no different from control (SMD -0.2 to 0.2 standard units). ^ indicates studies for which data transformation or imputation was required to include the result in the meta-analysis. This included crossover trials and studies that reported results as a dichotomous or ordinal outcome (identifiable because no mean or SD is reported for the study in the forest plot). * Denotes studies for which the direction of effect was changed to match the overall plot (e.g. positive numbers are beneficial)

Results of sensitivity analyses

Table D6.1 presents results for the original analysis (all studies, random effects model) and three 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

a. transforming or imputing statistics, or
b. 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 or imputing statistics was necessary, and then also removing studies for which change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Table D6.1. Sensitivity analyses for health-related quality of life outcome, both comparisons

Comparison[1]	Sensitivity analysis	Purpose of sensitivity analysis	No trials	Original effect (95% CI)	No trials	Sensitivity analysis effect
C1. AT (any mode) v inactive control (not massage)	No imputation or transformations[2]	Investigate robustness of MA effect	14	SMD 0.54 (0.13 to 0.94); I2 = 87%	11	SMD 0.57 (0.05 to 1.09); I2 = 90%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			8	SMD 0.36 (-0.25 to 0.97); I2 = 89%
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			14	SMD 0.35 (0.23 to 0.48); I2 = 81%
C2. AT (massage) v control (massage)	No imputation or transformations[2]	Investigate robustness of MA effect	12	SMD 0.34 (-0.07 to 0.75); I2 = 84%	11	SMD 0.33 (-0.10 to 0.77); I2 = 85%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect			8	SMD 0.36 (-0.25 to 0.97); I2 = 89%
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			12	SMD 0.27 (0.13 to 0.41); I2 = 80%

[1] C1. includes studies that compare AT (any mode, massage or not) to an inactive control that does not involve massage; C2 includes studies that compare AT (massage) to a massage control that is comparable to that used to deliver AT.

[2] This analysis was limited to trials that reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals

[3] 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. AT = aromatherapy; MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

Bias due to missing results from the meta-analysis

For Comparison 1 the combined effect estimated from the fixed effect model (SMD 0.35) was smaller than from the random effects model (SMD 0.54) (Table D6.1), but in both cases the effect estimate indicated an improvement in HR-QoL greater than the threshold for an important effect. The contour-enhanced funnel plot in Figure D6.2 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).

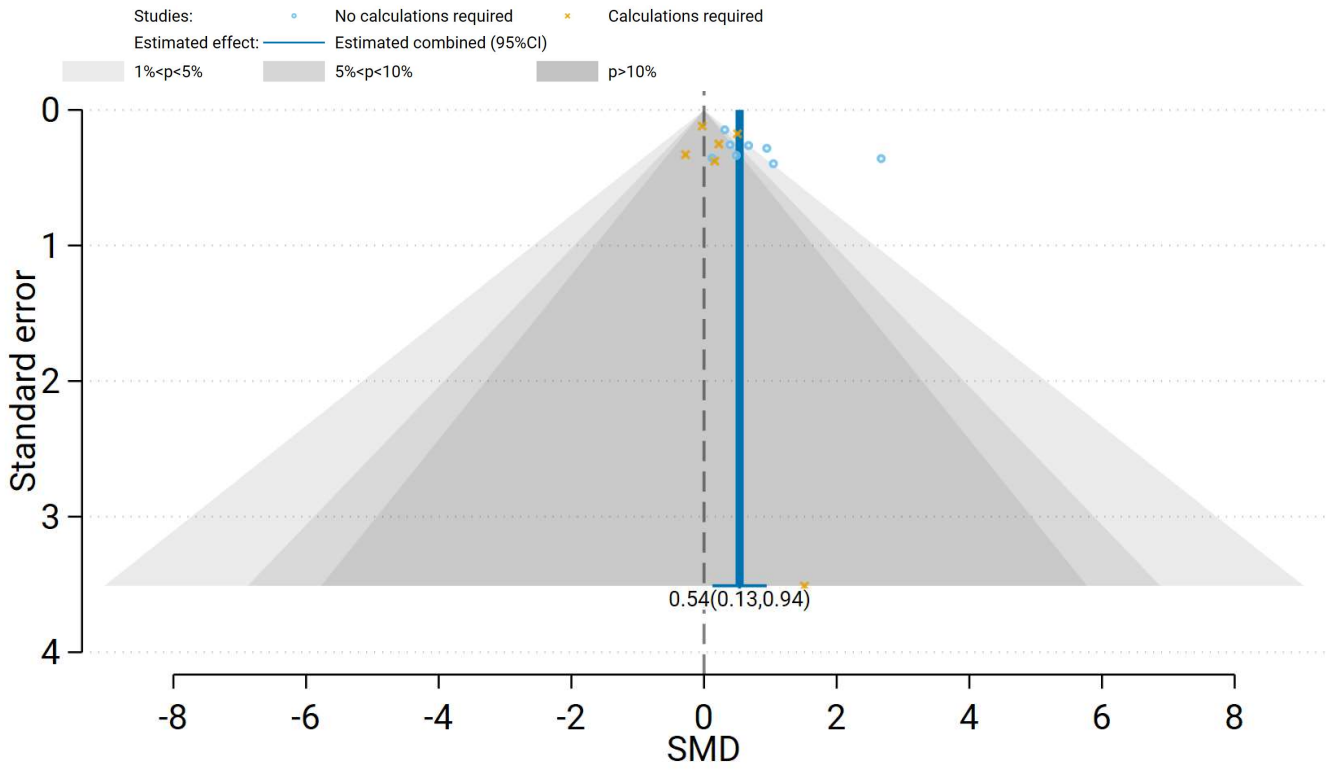

Fig D6.2 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on HR-QoL. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

Comparison 2: Aromatherapy (massage) versus inactive control (massage)

For the outcome health-related quality of life, 12 studies were included in the meta-analysis for Comparison 2 which compared aromatherapy delivered by massage to an inactive massage control (i.e. a comparable form of massage to that received by the intervention group).

Results of subgroup analyses

Population group

A single subgroup analysis was performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity). Specifically, whether the combined estimate of effect was importantly different for the different population groups contributing to the analysis (cancer and advanced disease, chronic conditions).

The subgroup analysis may partly explain some of the inconsistency observed in the overall analysis (i.e., differences in the direction or size of the observed effect) in Comparison 2. The test for subgroup differences was significant ($P < 0.008$); however, for the chronic conditions subgroup, the I^2 remains high, which appears largely due to differences in the magnitude of effect across studies rather than differences in the direction of effect. Results for this analysis are presented in the main report (Section 4.7, Figure 4.7.2).

Results of sensitivity analyses

Table D6.1 presents results for the original analysis (all studies, random effects model) and three sensitivity analyses for Comparison 2. The combined estimate of effect was similar in the original analysis and the sensitivity analyses removing studies for which transforming or imputing statistics was necessary, and when we removed any additional studies for which change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Bias due to missing results from the meta-analysis

The combined effect estimated from the fixed effect model (SMD 0.27) was similar to that from the random effects model (SMD 0.34) (Table D6.1). The contour-enhanced funnel plot in Figure D6.3 includes too few studies to provide any evidence about missing results (publication bias).

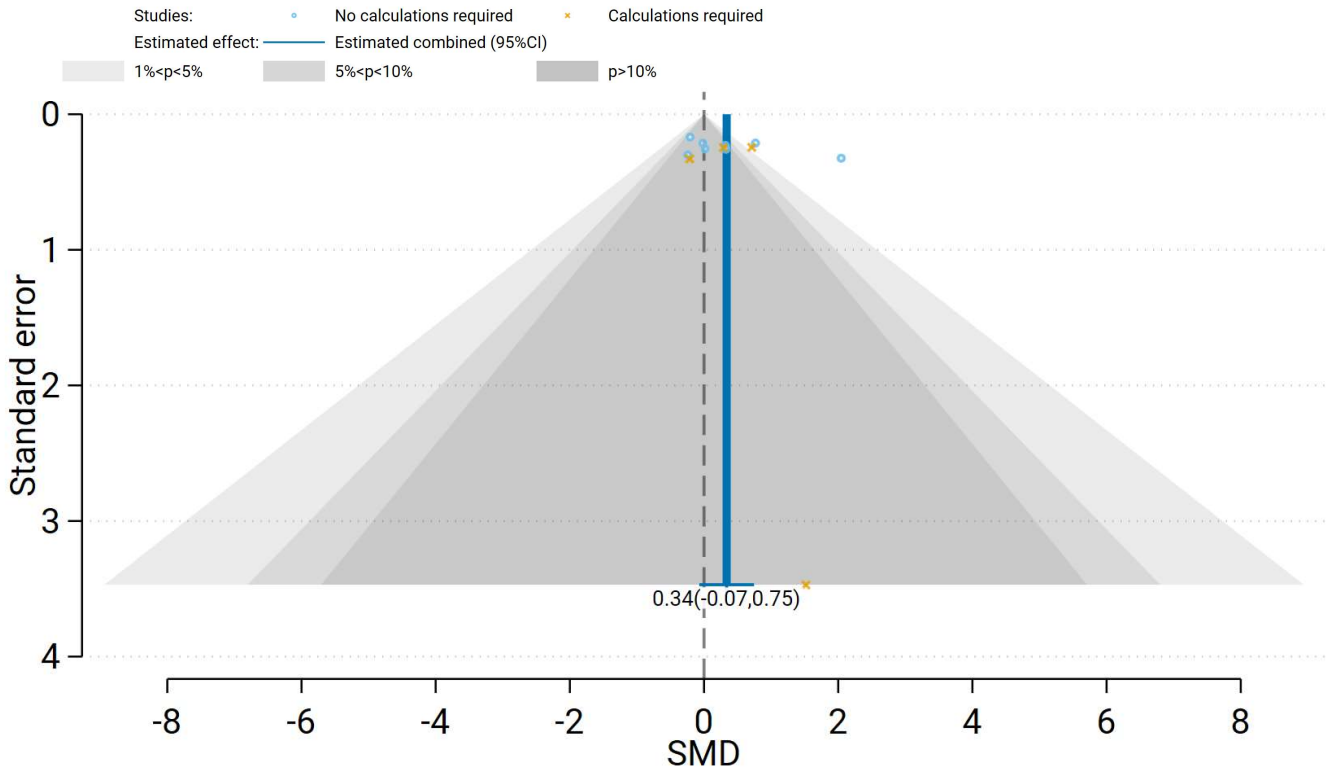

Fig D6.3 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 2. the effect of aromatherapy (massage) versus inactive control (massage) on HR-QoL. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

D7 Physical function

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

Comparison 1: Aromatherapy (any mode) versus inactive control (usual care, placebo, no intervention)

For the outcome physical function, 10 studies were included in the meta-analysis for Comparison 1 which compared aromatherapy delivered by any mode to an inactive control that did not involve massage (usual care, placebo, no intervention).

Results of subgroup analyses

The following subgroup analyses were performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity).

1. Population group (both comparisons): whether the combined estimate of effect was importantly different for different population groups (chronic musculoskeletal conditions, cancer and advanced disease, other chronic conditions).
2. Mode of aromatherapy delivery (Comparison 1 only): whether the combined estimate of effect was importantly different when aromatherapy was delivered by massage compared to another mode (inhalation, topical).

Neither of the subgroup analyses provided a credible explanation for any inconsistent effects observed across studies (i.e., differences in the direction or size of the observed effect) in Comparison 1.

Population group

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 < 0.005) but this was likely due to a very narrow confidence interval for the cancer subgroup which contained a single study. The estimates for the two subgroups that included multiple studies were identical and had completely overlapping confidence interval, and the I^2 indicated inconsistency within each subgroup. These results suggest that population group does not explain any observed inconsistency in the overall analysis.

Mode of aromatherapy delivery

Results for this analysis are presented in Figure D7.1. The test for subgroup differences was significant (P = 0.019). Results were relatively consistent when aromatherapy was delivered by massage (overlapping confidence intervals, I^2 = 27%), slightly less so in the inhalation subgroup. The effect is larger in the massage group (SMD=0.81) than in the inhalation group (SMD=0.23). This provides some evidence that mode of delivery may partially explain inconsistent effects across studies in the overall analysis. While the point estimates for each subgroup differ in size (SMD of 0.23 for inhalation/topical; SMD of 0.81 for massage), both estimates indicate an important improvement in physical function with aromatherapy and the confidence intervals for the subgroup estimates overlap.

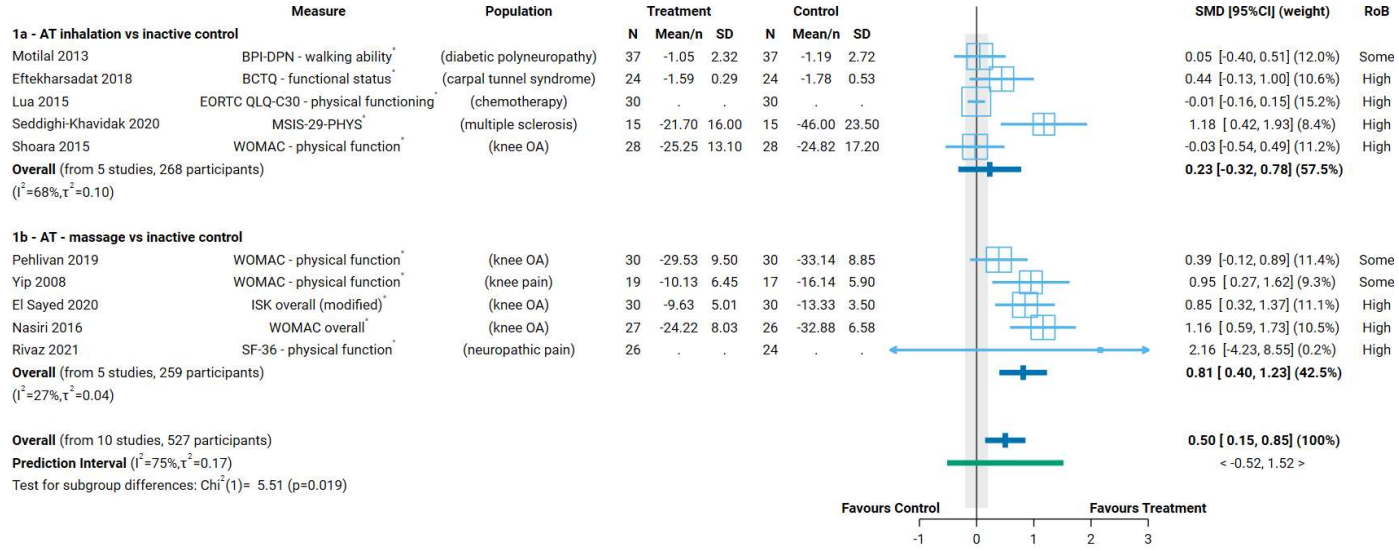

Fig D7.1 | Forest plot for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on physical function; subgrouped by mode of aromatherapy delivery. SMD = standardised mean difference. Blue lines show 95% confidence intervals (CI) and green lines show prediction intervals (PI). The shaded grey area indicates the pre-specified range where the effect of aromatherapy is considered to be no different from control (SMD -0.2 to 0.2 standard units). ^ indicates studies for which data transformation or imputation was required to include the result in the meta-analysis. This included crossover trials and studies that reported results as a dichotomous or ordinal outcome (identifiable because no mean or SD is reported for the study in the forest plot). * Denotes studies for which the direction of effect was changed to match the overall plot (e.g. positive numbers are beneficial)

Results of sensitivity analyses

Table D7.1 presents results for the original analysis (all studies, random effects model) and three 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
    a. transforming or imputing statistics, or
    b. 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 or imputing statistics was necessary. No additional studies were removed because change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Table D7.1. Sensitivity analyses for physical function outcome, both comparisons

Comparison[1]	Sensitivity analysis	Purpose of sensitivity analysis	No trials	Original effect (95% CI)	No trials	Sensitivity analysis effect
C1. AT (any mode) v inactive control (not massage)	No imputation or transformations[2]	Investigate robustness of MA effect	10	SMD 0.50 (0.15 to 0.85); I2 = 75%	8	SMD 0.58 (0.19 to 0.98); I2 = 64%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect				No additional studies removed.
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			10	SMD 0.20 (0.08 to 0.32); I2 = 76%
C2. AT (massage) v control (massage)	No imputation or transformations[2]	Investigate robustness of MA effect	7	SMD 0.45 (0.09 to 0.80); I2 = 48%	6	SMD 0.44 (0.04 to 0.84); I2 = 53%
	No imputation, transformations or change scores[3]	Investigate robustness of MA effect				No additional studies removed.
	Fixed effect analysis	Investigate small study effects (bias due to missing results)			7	SMD 0.46 (0.26 to 0.67); I2 = 44%

[1] C1. includes studies that compare AT (any mode, massage or not) to an inactive control that does not involve massage; C2 includes studies that compare AT (massage) to a massage control that is comparable to that used to deliver AT.

[2] This analysis was limited to trials that reported i) means and standard deviations, ii) means and standard errors, or iii) mean differences and their confidence intervals

[3] 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. AT = aromatherapy; MA = meta-analysis; SMD = standardised mean difference; CI = confidence interval

Bias due to missing results from the meta-analysis

For Comparison 1 the combined effect estimated from the fixed effect model (SMD 0.20) was smaller than from the random effects model (SMD 0.50) (Table D7.1), with the fixed effect estimate on the threshold between important improvement and little or no difference in physical function with aromatherapy. The contour-enhanced funnel plot in Figure D7.2 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, the number of studies is small so we cannot be confident that this is due to non-reporting bias.

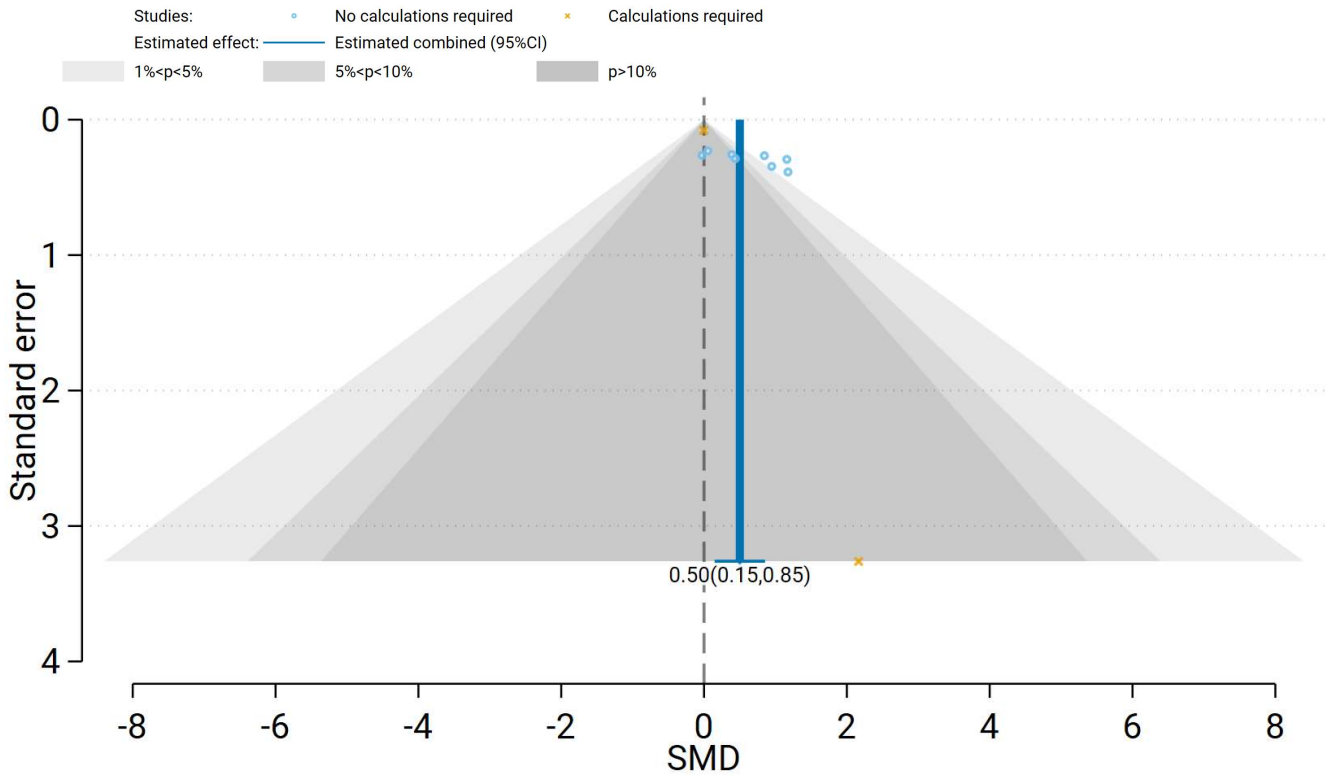

Fig D7.2 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 1. the effect of aromatherapy (any mode) versus inactive control (usual care, no intervention, placebo) on physical function. Shaded regions represent different categories of conventional milestone levels of statistical significance. SMD = standardised mean difference. Blue line shows the combined estimate from random effects model.

Comparison 2: Aromatherapy (massage) versus inactive control (massage)

For the outcome physical function, 7 studies were included in the meta-analysis for Comparison 2 which compared aromatherapy delivered by massage to an inactive massage control (i.e. a comparable form of massage to that received by the intervention group).

Results of subgroup analyses

Population group

A single subgroup analysis was performed to investigate whether there was a credible explanation for the inconsistent effects that were observed across studies (statistical heterogeneity). Specifically, whether the combined estimate of effect was importantly different for the different population groups contributing to the analysis (chronic musculoskeletal conditions, other chronic conditions).

Results for this analysis are presented in the main report (Section 4.8, Figure 4.8.2). The test for subgroup differences was not significant ($P < 0.399$), which is expected with only two subgroups. However, the point estimates for both subgroups was similar and the confidence intervals for these estimates were entirely overlapping. This suggests that the population group does not explain any inconsistency in the effects across studies in the overall analysis, which was minimal.

Results of sensitivity analyses

Table D7.1 presents results for the original analysis (all studies, random effects model) and two sensitivity analyses for Comparison 2. The combined estimate of effect was similar in the original analysis and the sensitivity analyses removing studies for which transforming or imputing statistics was necessary. No additional studies were removed because change scores were used. This indicates that the result was robust to the assumptions required to include these results.

Bias due to missing results from the meta-analysis

The combined effect estimated from the fixed effect model (SMD 0.46) was the same as that from the random effects model (SMD 0.45) (Table D7.1). The contour-enhanced funnel plot in Figure D7.3 includes too few studies to provide any evidence about missing results (publication bias).

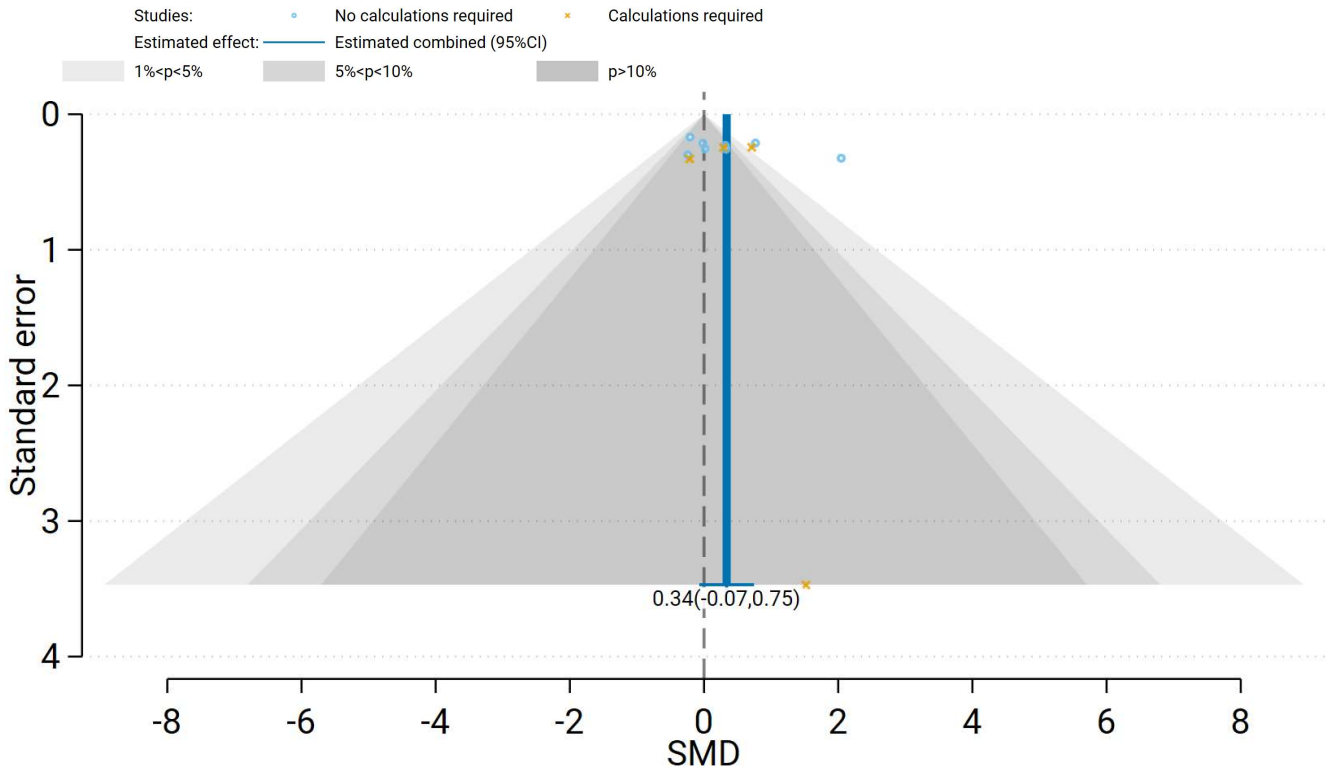

Fig D7.3 | Contour enhanced funnel plot of estimates of SMD versus their standard errors for Comparison 2. the effect of aromatherapy (massage) versus inactive control (massage) on physical function. Shaded regions represent different categories of conventional milestone levels of statistical significance. 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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