Supplementary Online Content

Feliciano JL, Waldfogel JM, Sharma R, et al. Pharmacologic interventions for breathlessness in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(2):e2037632. doi:10.1001/jamanetworkopen.2020.37632

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods details

Statistical heterogeneity

We evaluated statistical heterogeneity among studies using an I^2 statistic. We considered an I^2 value greater than 50% as substantial statistical heterogeneity. When we found substantial heterogeneity, we evaluated whether quantitative synthesis was appropriate or conducted sensitivity analysis when applicable.

Clinically Important Difference

Although a minimally clinically important difference (MCID) in breathlessness intensity has not been formally established, there are data available to help guide this determination. In heart failure, studies have identified a difference on the VAS between 10 and 21.1 mm as clinically significant[1-3]. Similarly, data for chronic refractory breathlessness and COPD suggest a difference of 10mm on the VAS or 0.8 on the Borg scale as clinically.[4,5] In a cancer population, data from a study of breathlessness from malignant pleural effusion suggest a difference on the VAS of 19mm is clinically significant and a population of advanced cancer patients admitted to a palliative care unit considered a difference on the NRS of 2.1 to be clinically important.[6,7]. Given the available data, we considered a difference on the VAS of 10mm or greater as clinically meaningful.

Cross-over Trials

For cross-over trials, we treated data similarly to parallel studies, using the measurement from the intervention periods and the measurements from the control periods Where possible we used a correlation co-efficient to impute a corrected standard of error, as this method may result in slightly wider confidence intervals.[8]

References

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eTable 1. Definitions of the grades of overall strength of evidence

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

eTable 2. Characteristics of included studies

Author, year Study design	Participants, n	Cancer type	Setting	Age	Followup	Breathlessness	Anxiety	Exercise capacity	HRQOL	Physiologic outcomes	Risk of bias
Placebo vs Anxiolytics											
Hardy, 2016[31] RCT	73	Cancer (not specified)	Hospital, Hospice (inpatient)	Median 70	14 days	X	X				Low
Peoples, 2016[21] RCT	379	Lung, Breast, Gastrointestinal, Other	Oncology clinic	62.9-64	28 days	X	X				Some concerns
Placebo vs Corticosteroids											
Hui, 2016[22] RCT	41	NSCLC, small cell lung cancer, Mesothelioma, other	Oncology, Palliative care clinic	63	14 days	X			X		Low
Placebo vs Opioids											
Bruera, 1993[20] RCT: Crossover	10	Lung (others not specified)	Not reported	NR	60 minutes	X				X	High
Charles, 2008[15] RCT: Crossover	20	Breast, Lung, Mesothelioma, Prostate, Renal	Hospice (home), Hospice (inpatient)	69	60 minutes	X				X	High
Hui, 2014[18] RCT	20	Breast, Gastrointestinal, Genitourinary, Gynecologic, Lung, Sarcoma	Oncology clinic	55	160 minutes	X		X		X	Low

Hui, 2016[17] RCT	24	Breast, Gastrointestinal, Genitourinary, Gynecologic, Lung, Hematologic, Other	Palliative care clinic	52.4	172 minutes	X		X		X	Low
Hui, 2017[16] RCT	20	Breast, GI, GU, Gyn, Lung, Other	Palliative care clinic	55	6 minutes	X		X		X	Low
Pinna, 2015[19] RCT: Crossover	13	Breast, Kidney, Lung, Stomach	Palliative care clinic	65.2	7 Days	X		X		X	Some concerns
Opioids vs Anxiolytics											
Navigante, 2010[25] RCT	63	Breast, Head and neck, Lung, Other	Oncology clinic	Range 30-82	5 Days	X				X	Some concerns
Opioids vs Anxiolytics vs Combination											
Navigane, 2006[26] RCT	101	Lung, Breast, Gynecologic, Sarcomas, Unknown primary, Colorectal, Other	Hospital	56.9-57.8	48 hours	X				X	High
Opioids vs Corticosteroids vs Bronchodilators											
Tian, 2016[29] Retrospective cohort	343	Breast, Colorectal, Gastric, Lung, Other (not specified)	Hospital	53.1-54.2	60 minutes	X				X	Serious
Opioids vs Opioids											
Aabom, 2019[32] RCT: Crossover	12	Lung and non-lung	Palliative care clinic	74.8	20 minutes	X					Low
Allard, 1999[28]	33	Breast, Lung/Pleura, Other (not specified)	Palliative care clinic	63.3	240 minutes	X				X	Some concerns

RCT											
Bruera, 2005[27] RCT: Crossover	12	Lung, Gastrointestinal, Other	Not reported	Median 58	2 days	X					High
Gamborg, 2013[24] RCT	20	NR	Hospice (inpatient)	NR	1 hour	X				X	High
Hui, 2019[30] RCT	30	Breast, Gastrointestinal, Genitourinary, Gynecological, Head and neck, Respiratory, Other (not specified)	Oncology, Palliative care clinic	52	NR	X				X	Low
Simon, 2016[23] RCT: Crossover	10	Lung, Hematology, Breast, Ovary, Esophagus, Melanoma	Inpatient	58	60 minutes	X				X	High

eTable 3. Summary of findings for the effects of pharmacological interventions on physiologic outcomes in patients with advanced cancer

Outcome	Comparison	Number of Studies Reporting Outcome (N)	Findings	Conclusion
Blood pressure				
	Opioid vs. placebo Fentanyl vs. placebo (2)	**2 RCTs** (N=44)	Pooled analysis: • Diastolic, SMD: 0.243; 95% CI, -0.23 to 1.41 • Systolic, SMD: 0.478; 95% CI, -0.13 to 1.09	• There was no difference between opioids and placebo in the effect on blood pressure
	Opioid vs. opioid High dose vs. low dose fentanyl	**1 RCTs** (N=30)	• Diastolic, difference between beginning and end of walk, calculated SMD: 0.14; 95% CI, -0.54 to 0.81 • Systolic, difference between beginning and end of walk, calculated SMD: 0.17; 95% CI, -0.51 to 0.84	• There was no significant change in blood pressure in patients in either arm
Heart rate				
	Opioids vs. placebo Fentanyl vs. placebo (2) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)	**3 RCTs** (N=64)	Pooled analysis with Charles, 2008 et al.[12] saline vs. nebulized hydromorphone comparison: • SMD: -0.14 (95% CI: -0.57 to 0.29), • I-squared=0.0%, p=0.66 Pooled analysis with Charles, 2008 et al.[12] saline vs. systemic hydromorphone comparison: • SMD: -0.03 (95% CI: -0.46 to 0.4) • I-squared=0.0%, p=0.46	• There was no significant difference between opioids and placebo in the effect on heart rate.
	Opioid vs. opioid sublingual vs. subcutaneous morphine (1) High dose vs. low dose fentanyl (1) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)	**3 RCTs** (N=75)	Pooled analysis: • SMD: 0.11; 95% CI, -0.3 to 0.52 • I-squared=0.0%, p=0.79	• There was no significant difference between opioids in the effect on heart rate
Oxygen saturation				
	Opioid vs. placebo Fentanyl vs. placebo (4) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1) Morphine vs. placebo	**6 RCTs** (N=107)	Pooled analysis with Charles, 2008 et al.[12] saline vs. nebulized hydromorphone comparison: • SMD: -0.07 (95% CI: -0.40 to 0.25), • I-squared=0.0%, p=0.65 Pooled analysis with Charles, 2008 et al.[1] saline vs. systemic	• There was no difference between opioids and placebo in the effect on oxygen saturation.

	(1)		hydromorphone comparison: • SMD: -0.13 (95% CI: -0.45 to 0.19) • I-squared=0.0%, p=0.63	
	Opioid vs. opioid Fentanyl vs. morphine (1) High dose vs. low dose fentanyl (1) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)	3 RCTs (N=65)	Pooled analysis: • SMD: -0.03; 95% CI, -0.44 to 0.37 • I-squared=0.0%, p=0.60	• There was no difference in the effect on oxygen saturation between opioids.
	Opioid vs. anxiolytics Oral morphine vs. oral midazolam (1) Subcutaneous morphine vs. subcutaneous midazolam vs. combination (1)	2 RCTs (N=164)	90 minutes (calculated SMD: 0.001, 95% CI, -0.49 to 0.5) or Day 5 (calculated SMD: -0.003, 95% CI, -0.5 to 0.49) Second study reported no significant differences between groups. Unable to calculate SMD, no variability reported	• There was no difference in the effect on oxygen saturation for opioids compared to anxiolytics
Respiratory rate				
	Opioid vs. placebo Fentanyl vs. placebo (3) Hydromorphone (nebulized) vs. hydromorphone (Oral or subcutaneous) vs. placebo (nebulized) (1) Morphine vs. placebo (**1**)	**5 RCTs** (N=94)	Pooled analysis with Charles, 2008 et al.[12] saline vs. nebulized hydromorphone comparison: • SMD: 0.11 (95% CI: -0.25 to 0.47), • I-squared=0.0%, p=0.44 Pooled analysis with Charles, 2008 et al.[12] saline vs. systemic hydromorphone comparison: • SMD: 0.05 (95% CI: -0.31 to 0.41) • I-squared=1.0%, p=0.40	• There was no difference between opioids and placebo in the effect on respiratory rate.
	Opioid vs. opioid Low dose vs. high dose opioid (drug unspecified) (1) Morphine vs. fentanyl (**1**) High dose vs. low dose fentanyl (1) Hydromorphone (nebulized) vs. hydromorphone (Oral or SC) vs. placebo (nebulized) (1)	**4 RCTs** (N=98)	Pooled analysis: • SMD: -0.23 (95% CI, -0.63 to 0.18) • I-squared=0.0%, p=0.91	• There was no difference between opioids in the effect on respiratory rate

SMD: standardized mean difference, RR: relative risk, MBGD: mean between group difference; vs= versus

eTable 4. List of studies reporting harms and dropouts in studies of pharmacological interventions for breathlessness in patients with advanced cancer

Author, year	N	Central nervous system	Gastro-intestinal	Pruritus	Urinary retention	Dry mouth	Dropouts
Opioids vs. Placebo							
Hui, 2017[16]	20	X	X	X			X
Hui, 2016[17]	24	X	X				
Hui, 2014[18]	20	X	X	X			
Pinna, 2015[19]	13		X				
Charles, 2008[15]	20						X
Anxiolytics vs. Placebo							
Peoples, 2016[21]	379						X
Hardy, 2016[31]	73	X					
Placebo vs. Corticosteroids vs. Placebo							
Hui, 2016[22]	41	X	X				X
Opioids vs. Opioids							
Kawabata, 2013[33] [retro]	95	X	X	X	X		
Bruera, 2005[27]	12	X	X				
Hui, 2019[30]	30	X	X	X			
Opioids vs. Anxiolytics							
Navigante, 2010[25]	63	X	X	X		X	X
Opioids vs. Anxiolytics vs. Combination							
Navigane, 2006[26]	101	X	X			X	
Opioids vs. Corticosteroids vs. Bronchodilators							
Tian, 2016[29]	343	X	X			X	

N=sample size

eTable 5. Rate of dropouts due to adverse effects of pharmacological interventions for breathlessness in patients with advanced cancer

Drug Class	Intervention	Dropouts due to adverse effects, n (%)
Opioids	Fentanyl[16]	1 (9.1%)
	Hydromorphone[15]	4 (16%)
	Morphine[25]	1 (3.2%)
Anxiolytics	Midazolam[25]	1 (3.2%)
	Buspirone[21]	10 (4.7%)
Corticosteroids	Dexamethasone[22]	1 (5.6%) – 1 (7.1%)

eTable 6a. Risk of bias of randomized controlled trials that evaluate the effects of pharmacologic interventions

Author, year	Domain 1: Randomization process	Domain 2: Deviations intended interventions (effect of assignment to intervention)	Domain 2: Deviations intended interventions (effect of adhering to intervention)	Domain 3: Missing outcome data	Domain 4: Measurement of the outcome	Domain 5: Selection of the reported result	Final Assessment
Aabom, 2019[32]	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Allard, 1999[28]	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns
Bruera, 1993[20]	Some concerns	Low risk	NA	Low risk	High risk	Low risk	High risk
Bruera, 2005[27]	Some concerns	Low risk	NA	Some concerns	Low risk	Some concerns	High risk
Charles, 2008[15]	Some concerns	Low risk	NA	Low risk	Low risk	Some concerns	High risk
Gamborg, 2013[24]	Some concerns	Some concerns	NA	Low risk	Some concerns	Low risk	High risk
Hardy, 2016[31]	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2014[18]	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2016[17]	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2016[22]	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2017[16]	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Hui, 2019[30]	Low risk	Low risk	NA	Low risk	Low risk	Low risk	Low risk
Navigante, 2006[26]	Low risk	Some concerns	NA	Low risk	Some concerns	Some concerns	High risk
Navigante, 2010[25]	Low risk	Some concerns	NA	Low risk	Some concerns	Some concerns	Some concerns

Peoples, 2016[21]	Low risk	Low risk	NA	Some concerns	Low risk	Low risk	Some concerns
Pinna, 2015[19]	Some concerns	Low risk	NA	Low risk	Low risk	Low risk	Some concerns
Simon, 2016[23]	Some concerns	Low risk	NA	Some concerns	High risk	High risk	High risk

eTable 6b. Risk of bias of observational studies that evaluate the effects of pharmacologic interventions

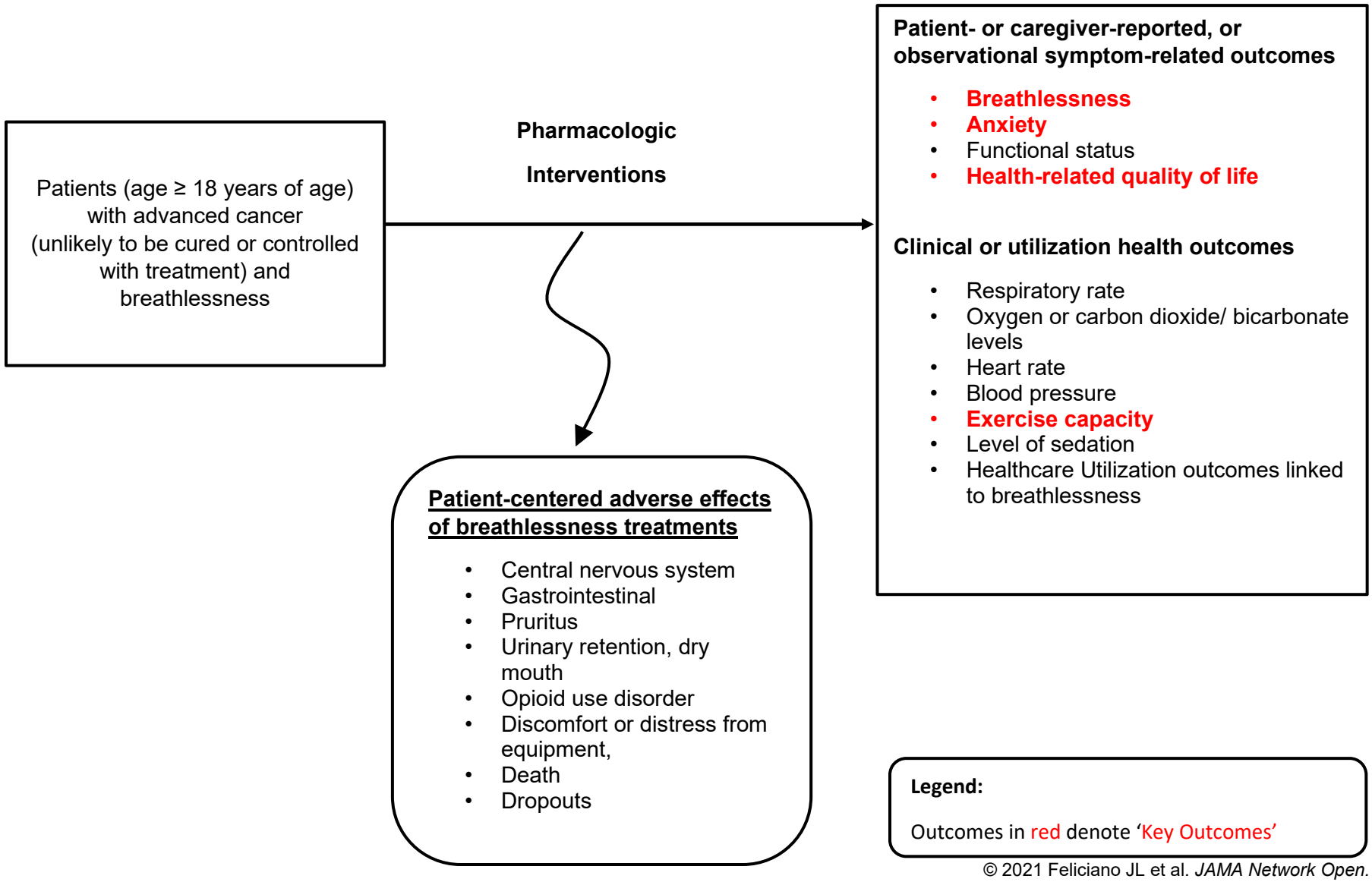
Author, year	Domain 1: Confounding	Domain 2: Patient Selection	Domain 3: Classifying Interventions	Domain 4: Deviations from intended interventions	Domain 5: Missing data	Domain 6: Measurement of outcomes	Domain 7: Selection of reported results	Overall Assessment
Kawabata, 2013[33]	Critical	Serious	Low	No information	Moderate	Moderate	Serious	Critical
Tian, 2016[29]	Serious	Moderate	Low	Moderate	Moderate	Moderate	Serious	Serious

eTable 7. Strength of evidence of studies that evaluate the effects of pharmacologic interventions

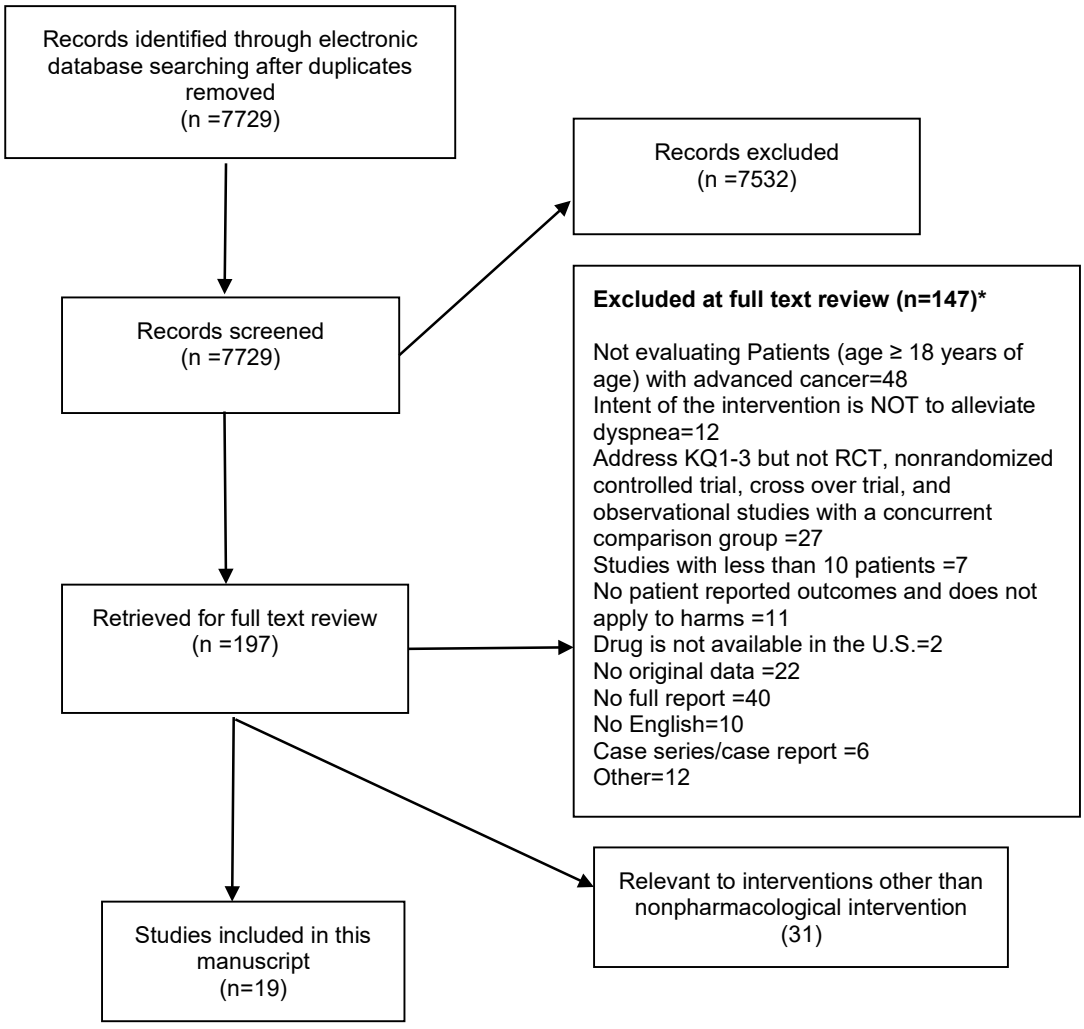
Key Outcome	Intervention	Number of studies (participants)	Study limitations	Directness	Consistency	Precision	Reporting bias	Strength of evidence
Breathlessness	Opioids vs Placebo	6 RCT (107 participants)	Low	Direct	Consistent	Precise	Undetected	Moderate
Breathlessness	Anxiolytics vs Placebo	2 RCT (452 participants)	Medium	Direct	Consistent	Imprecise	Undetected	Low
Breathlessness	Corticosteroids vs Placebo	1 RCT (41 participants)	Low	Direct	Unknown	Imprecise	Suspected	Insufficient
Breathlessness	Opioids vs Opioids	7 RCT (142 participants)	High	Direct	Consistent	Imprecise	Suspected	Low
Breathlessness	Opioids vs Anxiolytics	2 RCT (164 participants)	Medium	Direct	Inconsistent	Imprecise	Suspected	Low
Breathlessness	Opioids vs Corticosteroids vs Bronchodilators	1 retrospective cohort (343 participants)	High	Direct	Unknown	Imprecise	Suspected	Insufficient
Anxiety	Anxiolytics vs Placebo	2 RCT (452 participants)	Medium	Direct	Consistent	Precise	Undetected	Low
Health-related quality of life	Corticosteroids vs Placebo	1 RCT (41 participants)	Low	Direct	Unknown	Imprecise	Suspected	Insufficient
Exercise capacity	Opioids vs Placebo	4 RCT (77 participants)	Low	Direct	Consistent	Precise	Undetected	Moderate

RCT=randomized clinical trial

eFigure 1. Analytic Framework for Evaluating Interventions for Breathlessness in Patients with Advanced Cancer

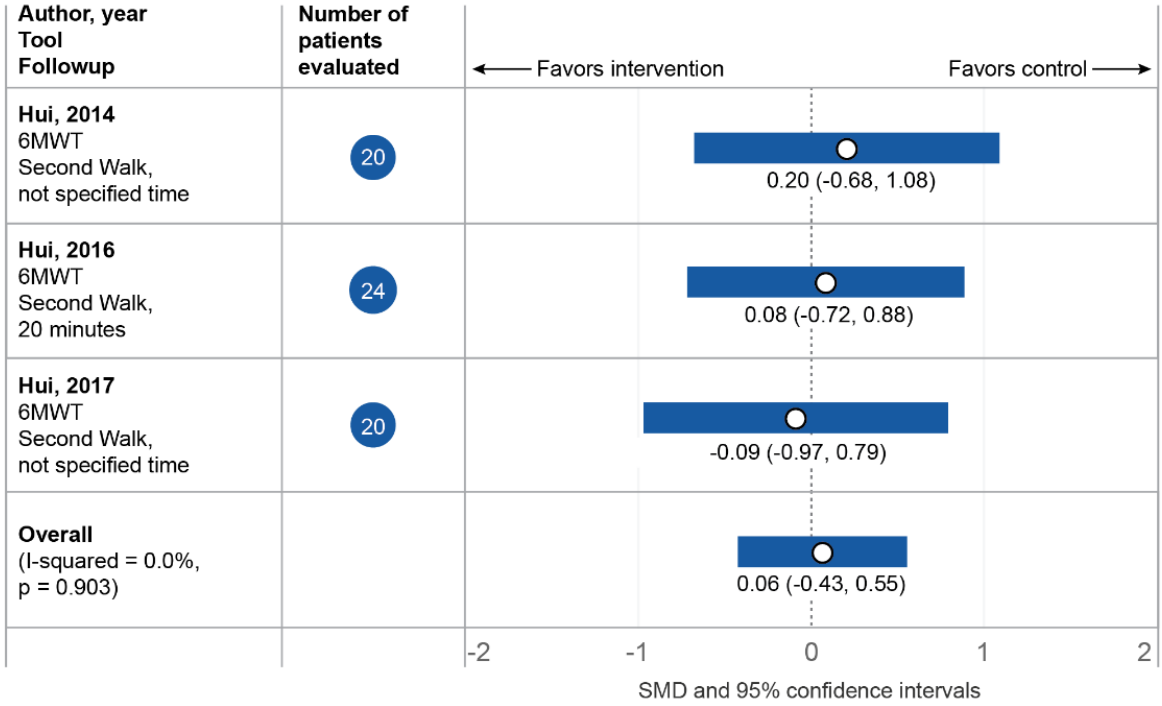


eFigure 2. Study Search and Preferred Reporting Items for Systematic Reviews and Meta-analyses Flowchart



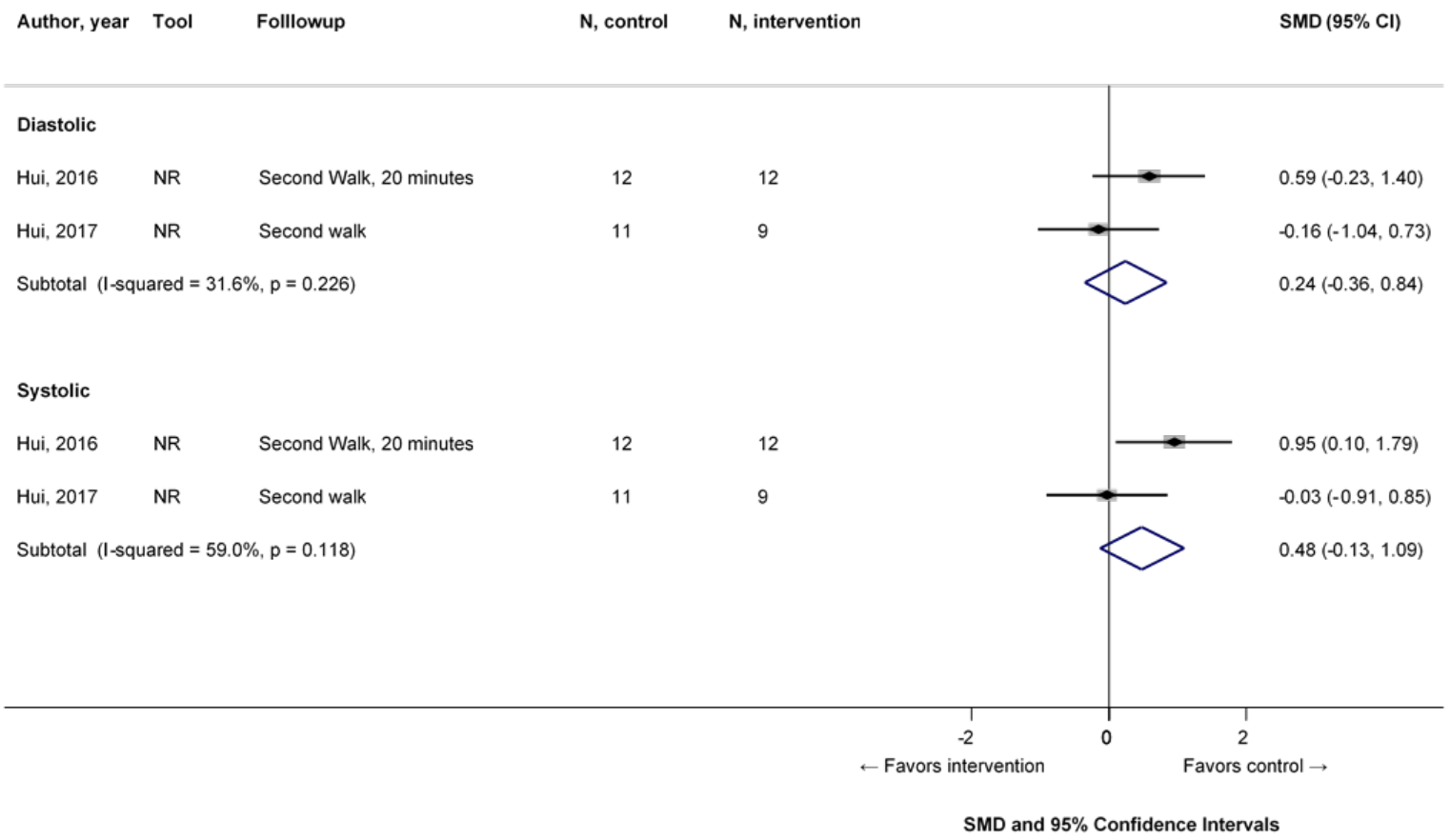
* Total exceeds the number of citations in the exclusion box, because citations could be excluded for more than one reason

eFigure 3. Meta-analysis of the effects on exercise capacity measures in randomized controlled trials comparing opioids with placebo in patients with advanced cancer



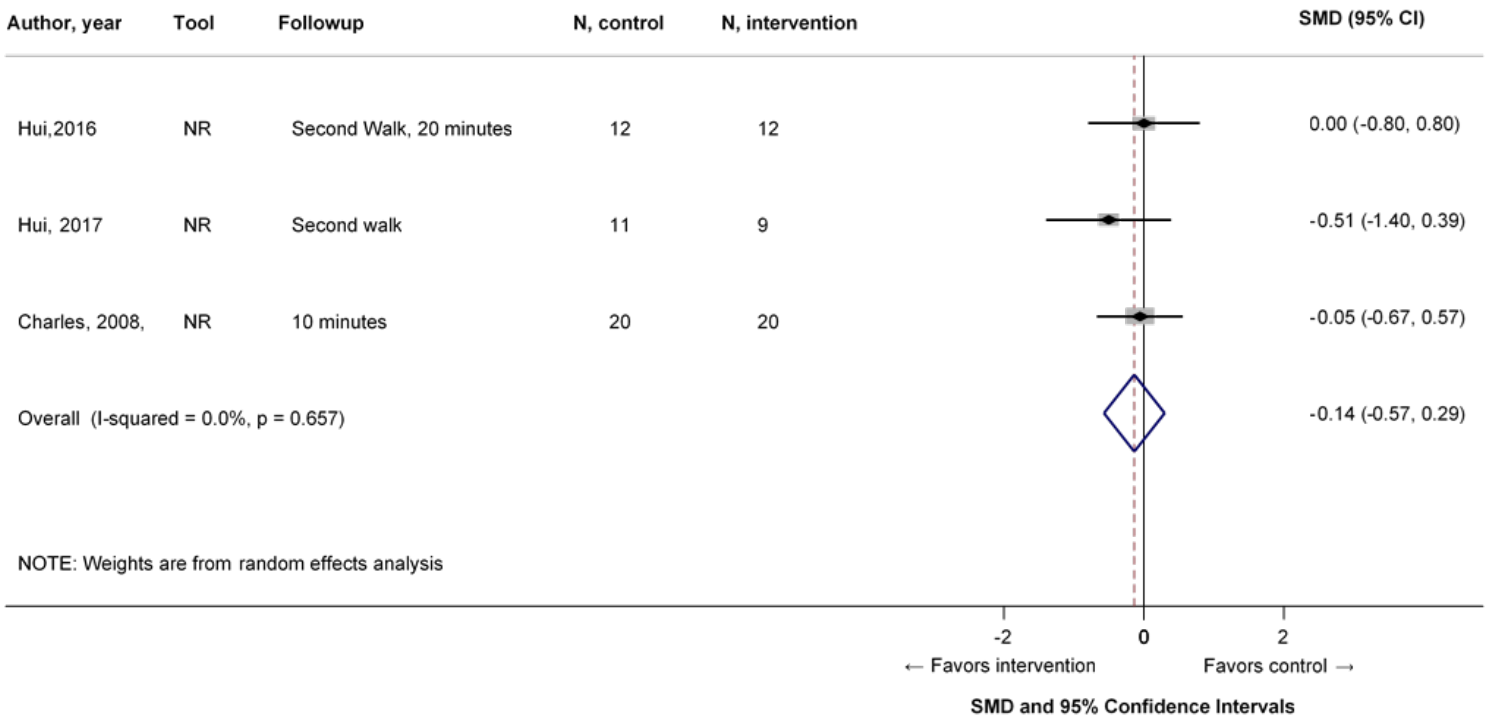
Blue dot size=corresponds to study size, Blue diamond=the result when all the individual studies are combined and averaged Length of the bar=corresponds to range of confidence interval.

eFigure 4. Meta-analysis of the effects of placebo vs opioids on blood pressure in patients with advanced cancer in inpatient hospice or palliative care units



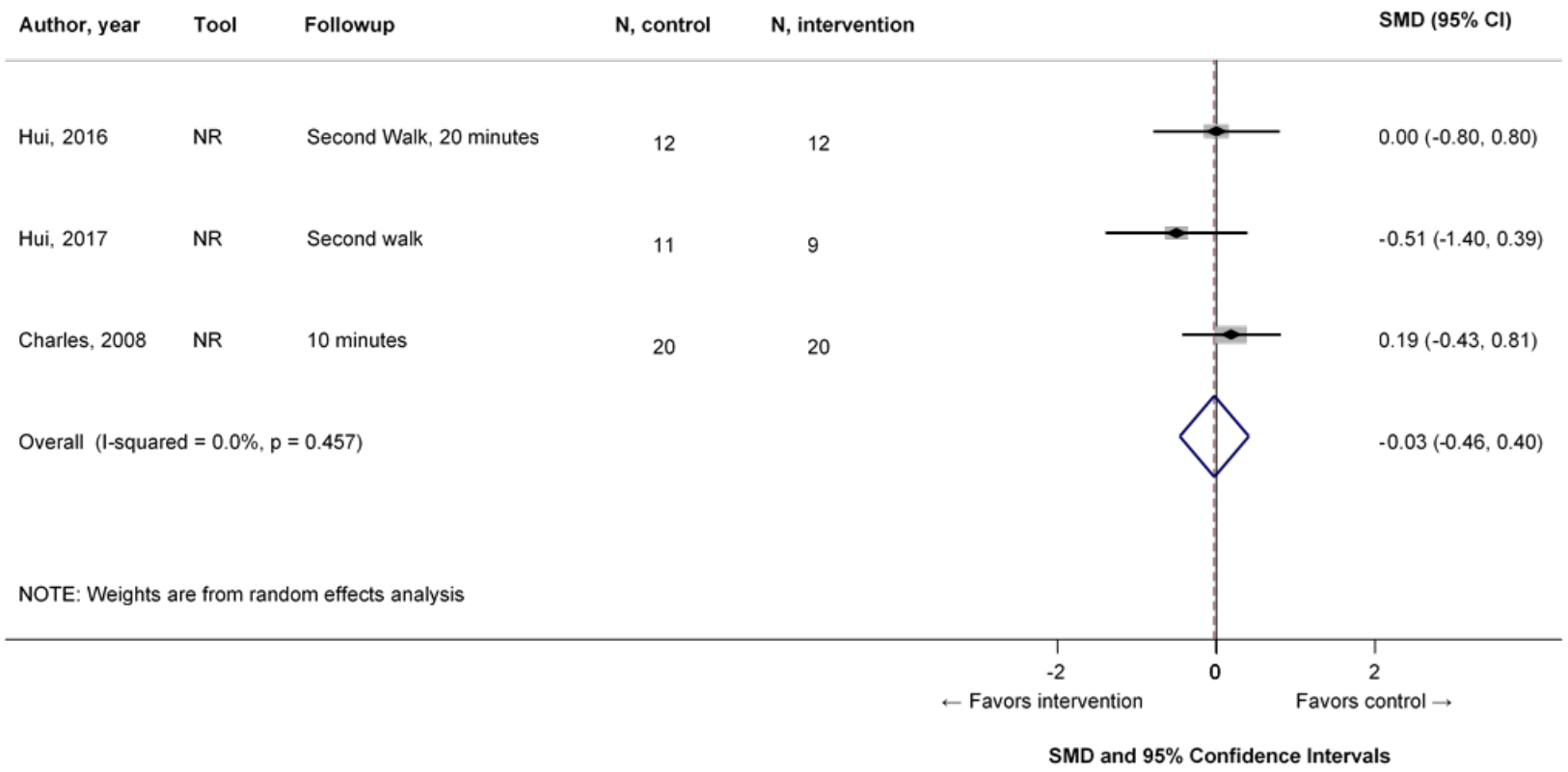
CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

eFigure 5. Meta-analysis of the effects of placebo vs opioids on heart rate in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.[15] saline vs nebulized hydromorphone comparison)



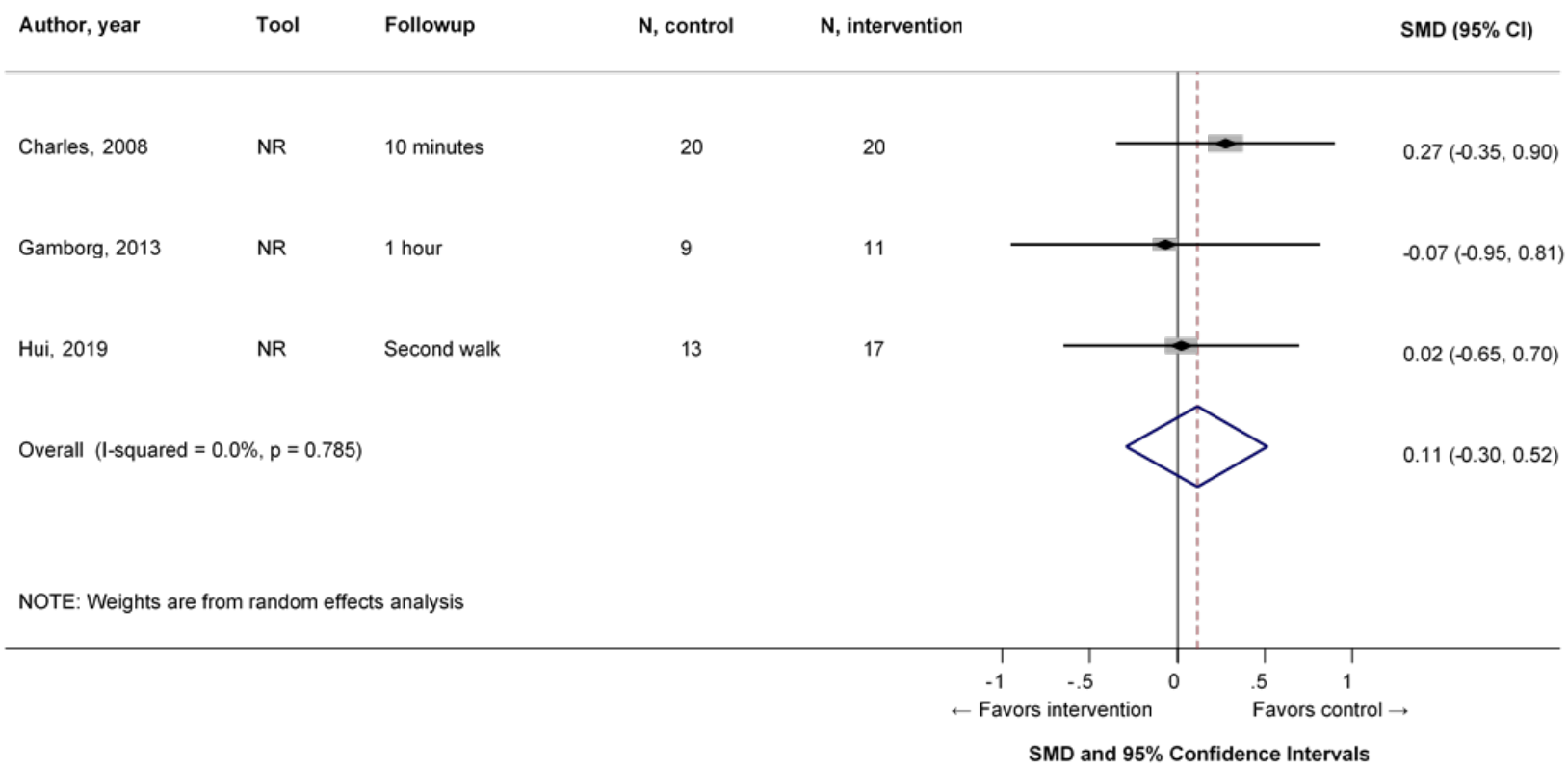
CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

eFigure 6. Meta-analysis of the effects of placebo vs opioids on heart rate in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.[15] saline vs systemic hydromorphone comparison)



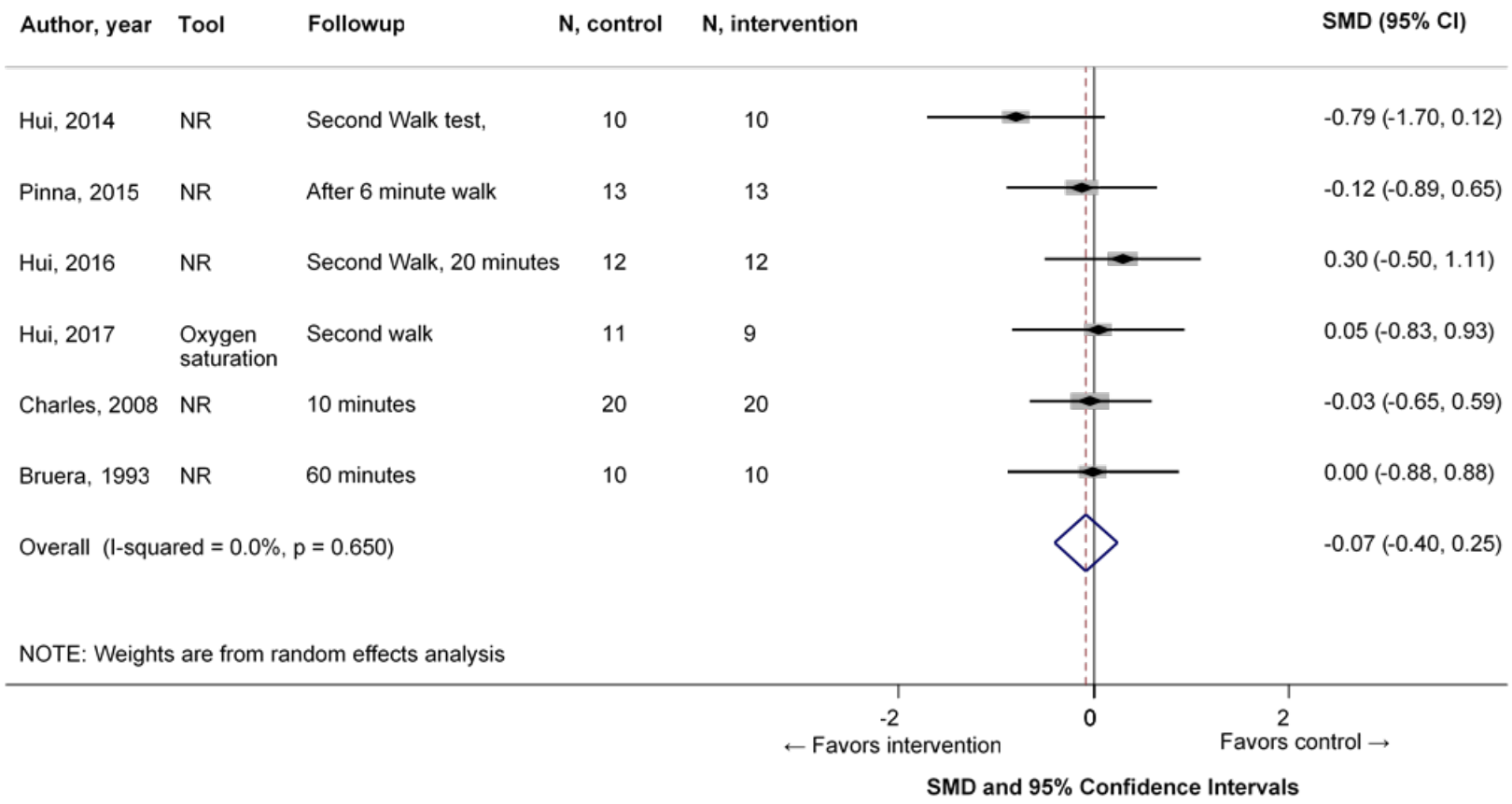
CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

eFigure 7. Meta-analysis of the effects of opioids vs opioids on heart rate in patients with advanced cancer in inpatient hospice or palliative care units



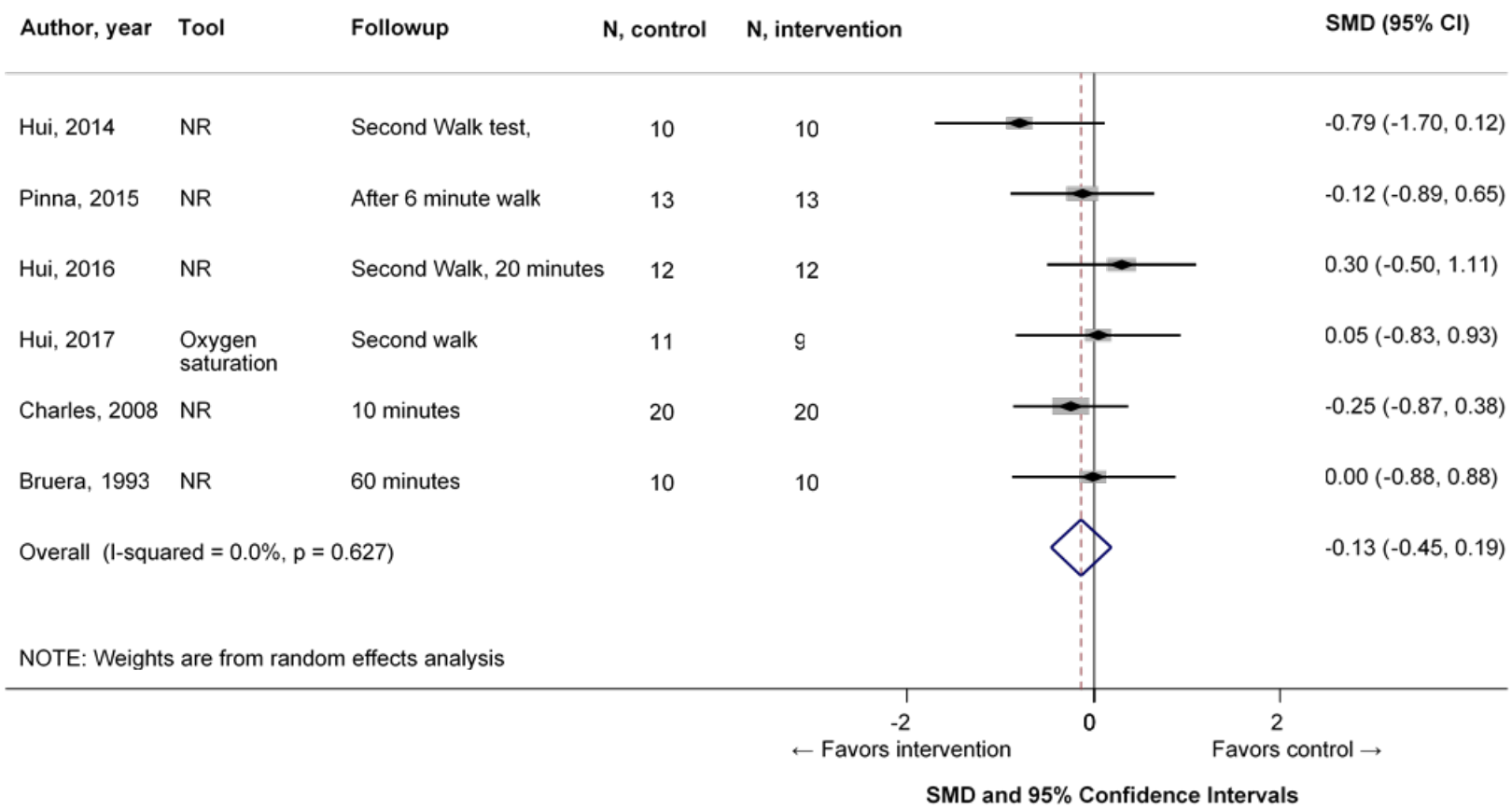
CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

eFigure 8. Meta-analysis of the effects of placebo vs opioids on oxygen saturation in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.[15] saline vs nebulized hydromorphone comparison)



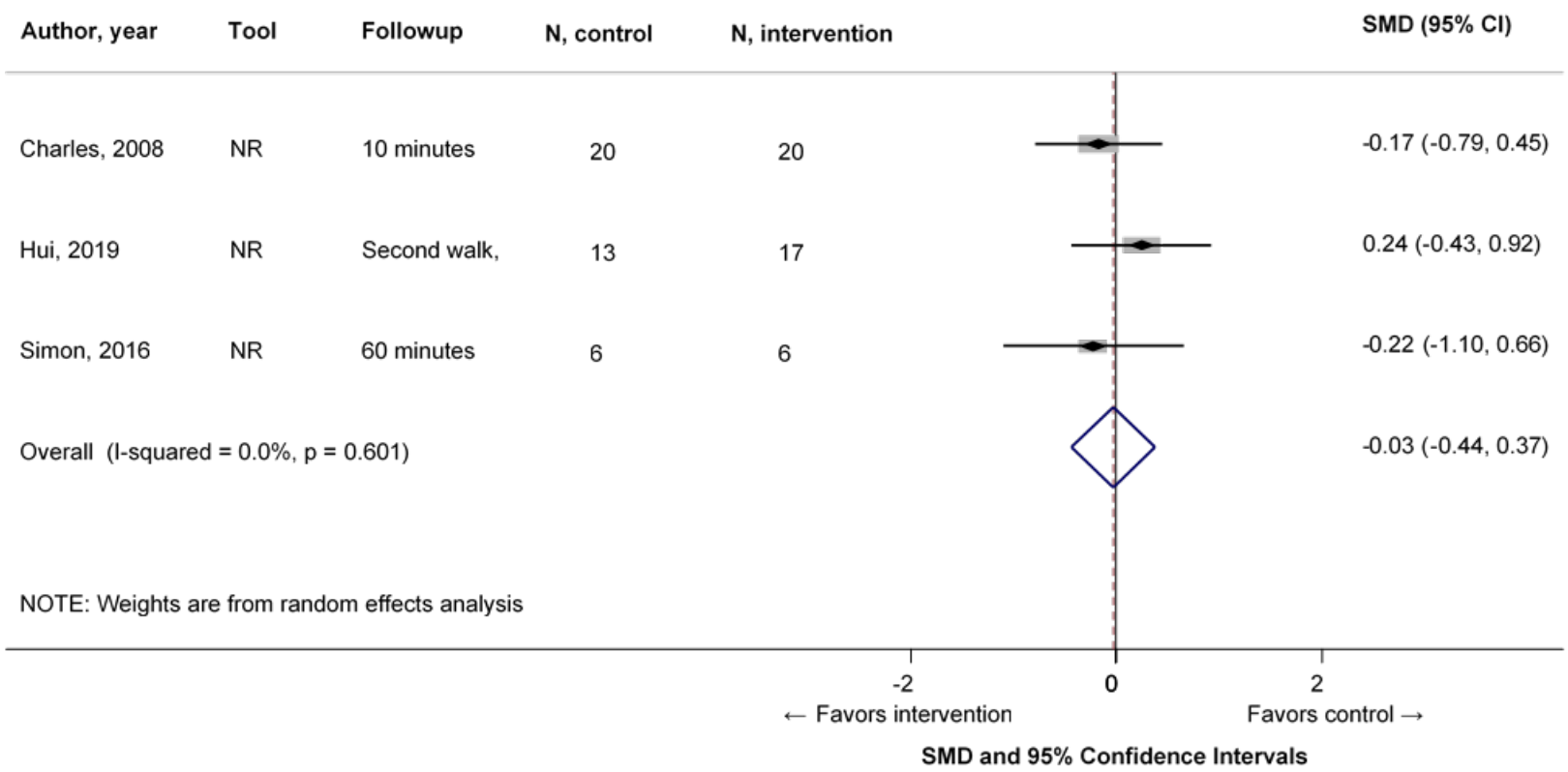
CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

eFigure 9. Meta-analysis of the effects of placebo vs opioids on oxygen saturation in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.[15] saline vs systemic hydromorphone comparison)



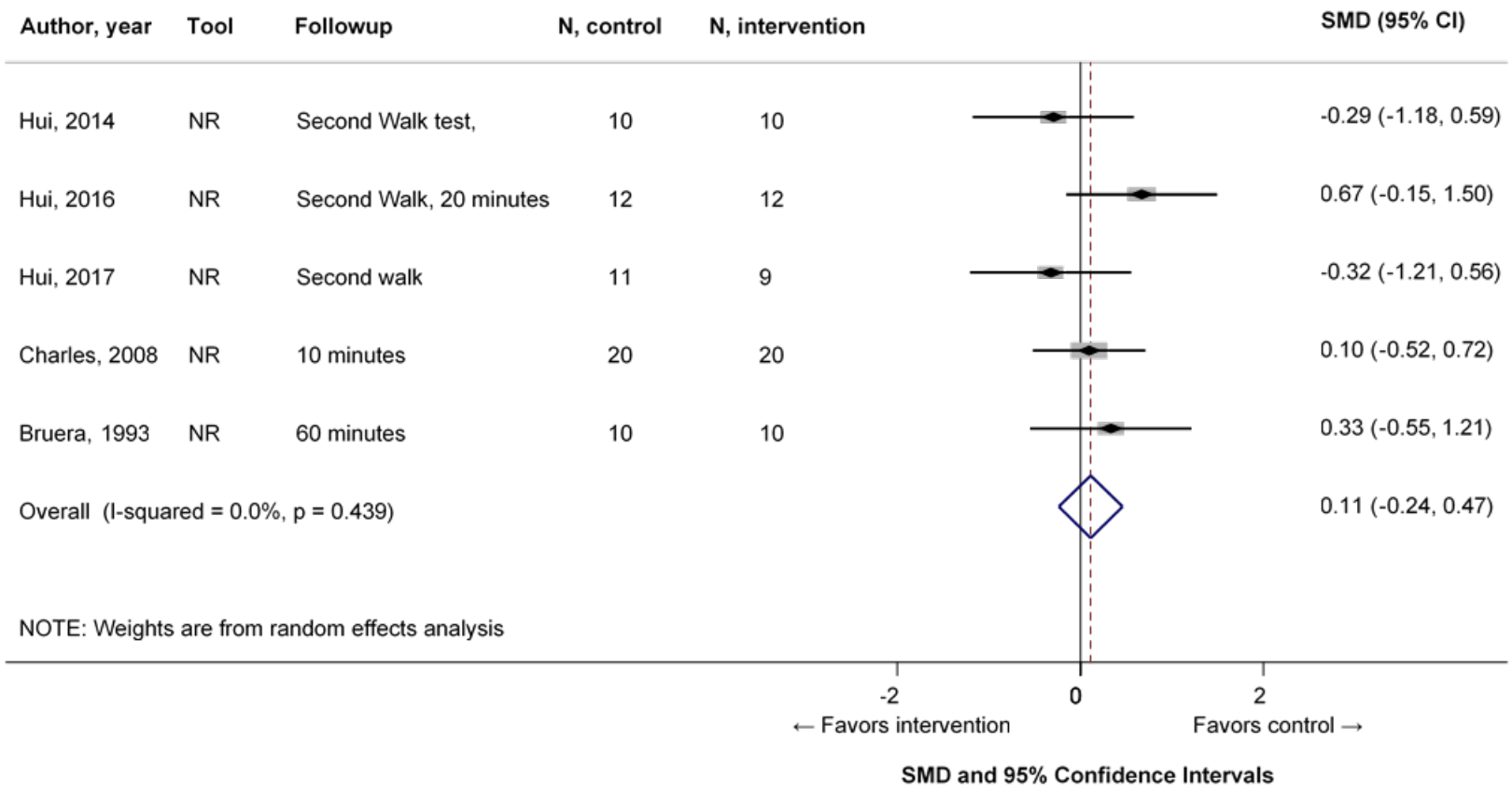
CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

eFigure 10. Meta-analysis of the effects of opioids vs opioids on oxygen saturation in patients with advanced cancer in inpatient hospice or palliative care units



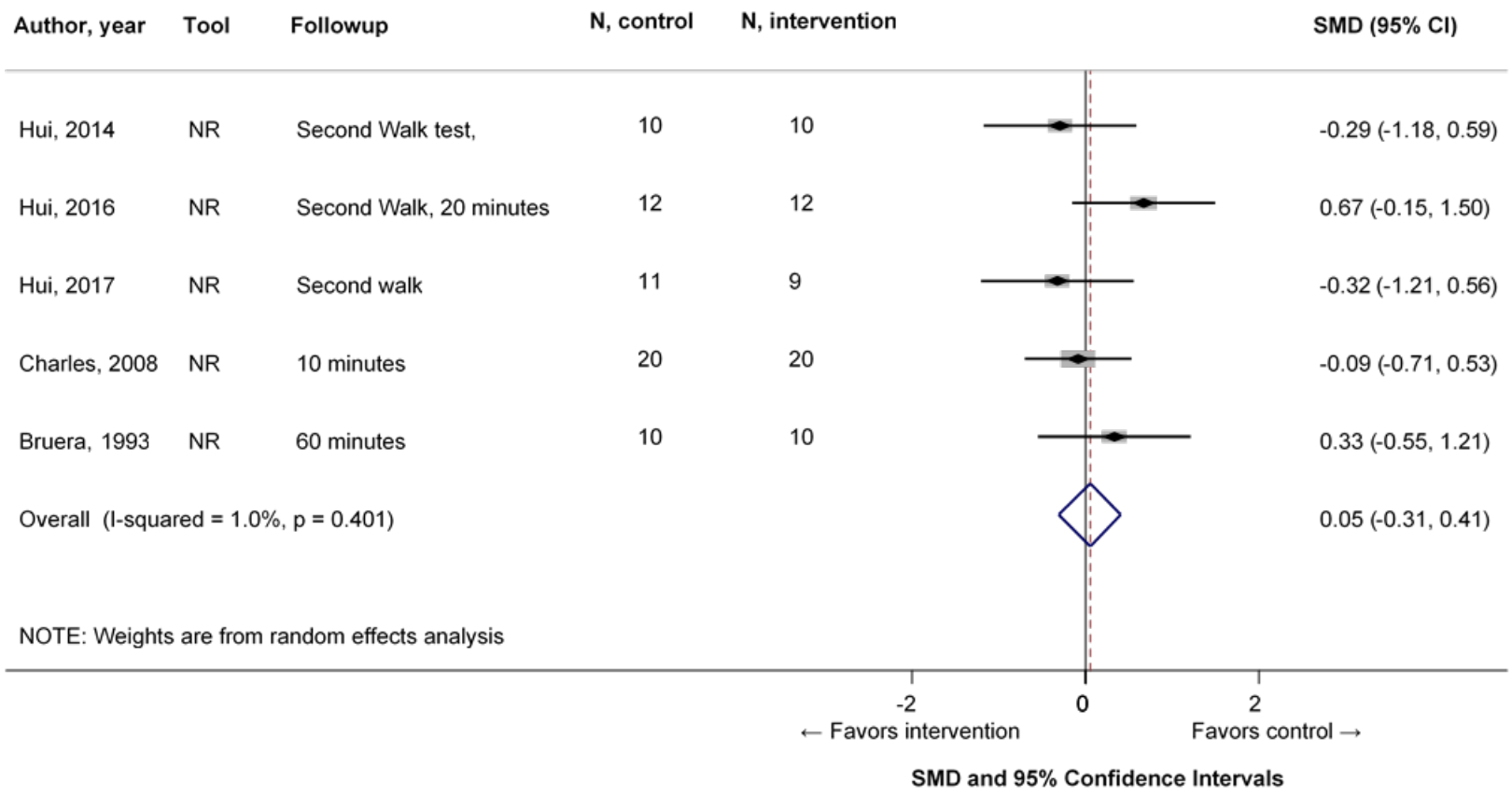
CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

eFigure 11. Meta-analysis of the effects of placebo vs opioids on respiratory rates in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.[15] saline vs nebulized hydromorphone comparison)



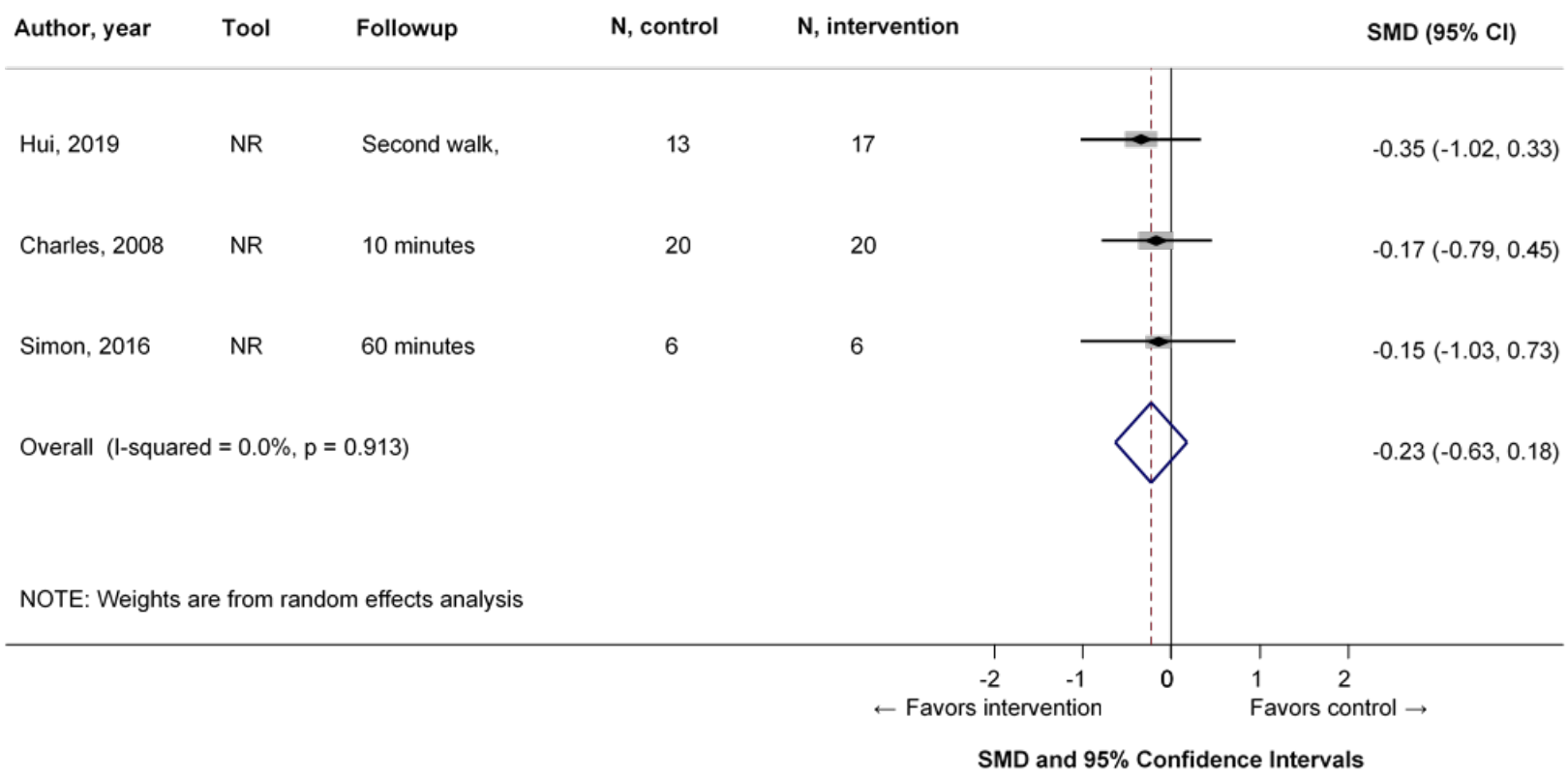
CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

eFigure 12. Meta-analysis of the effects of placebo vs opioids on respiratory rates in patients with advanced cancer in inpatient hospice or palliative care units (Charles, 2008 et al.[15] saline vs systemic hydromorphone comparison)



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

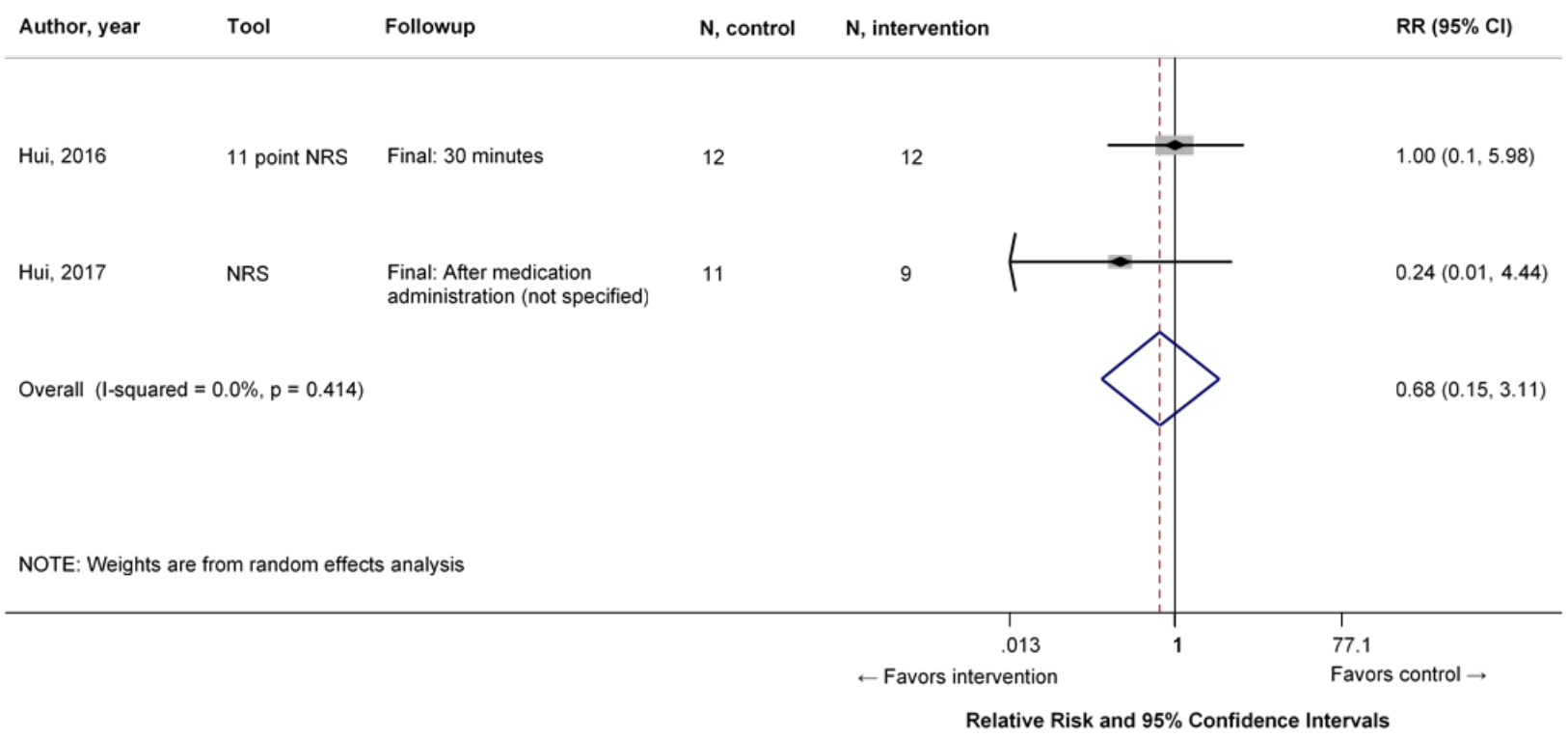
eFigure 13. Meta-analysis of the effects of opioids vs opioids on respiratory rates in patients with advanced cancer in inpatient hospice or palliative care units



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference

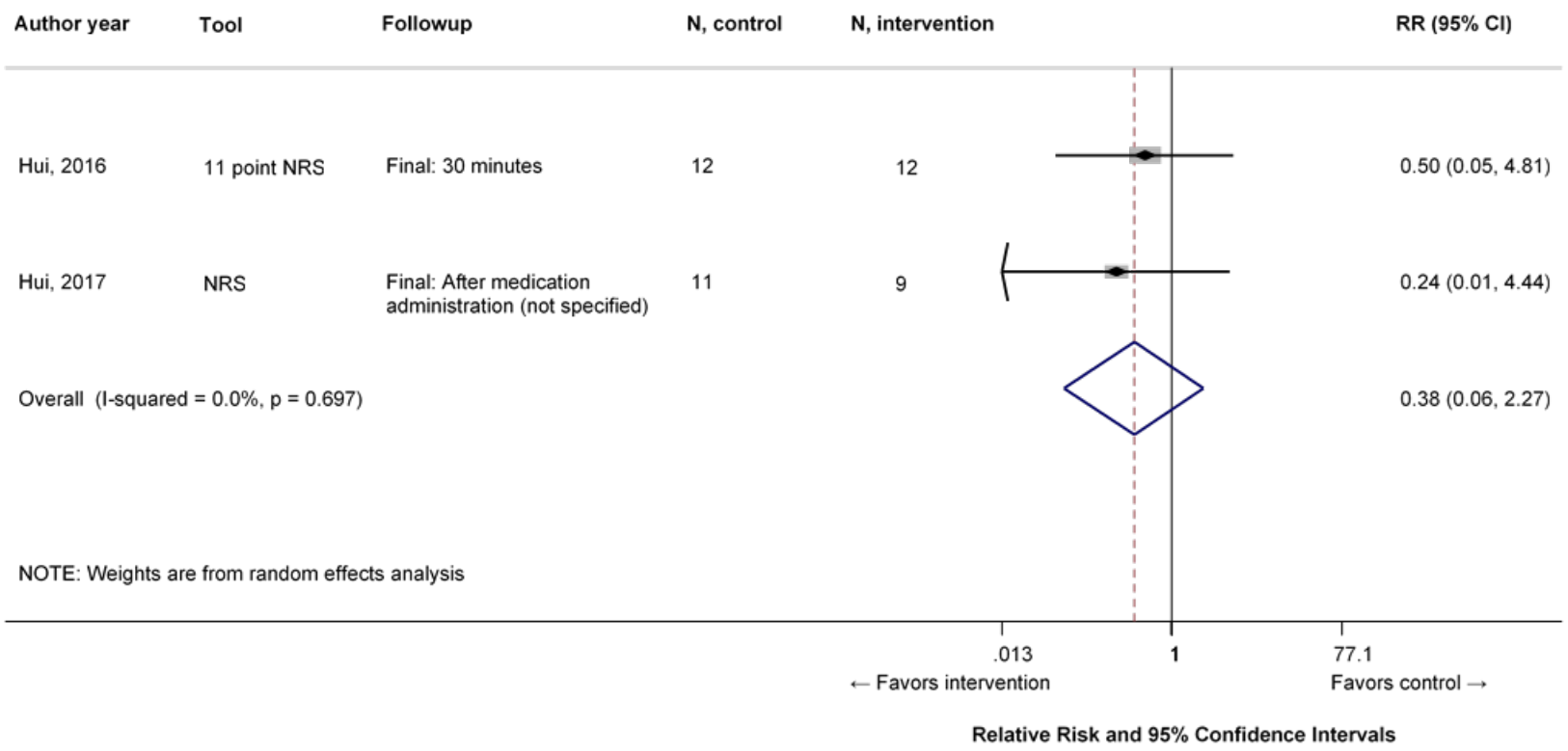
Meta-analysis of harms of pharmacological interventions

eFigure 14. Meta-analysis of the effects of placebo vs opioids on dizziness outcomes in patients with advanced cancer in inpatient hospice or palliative care units



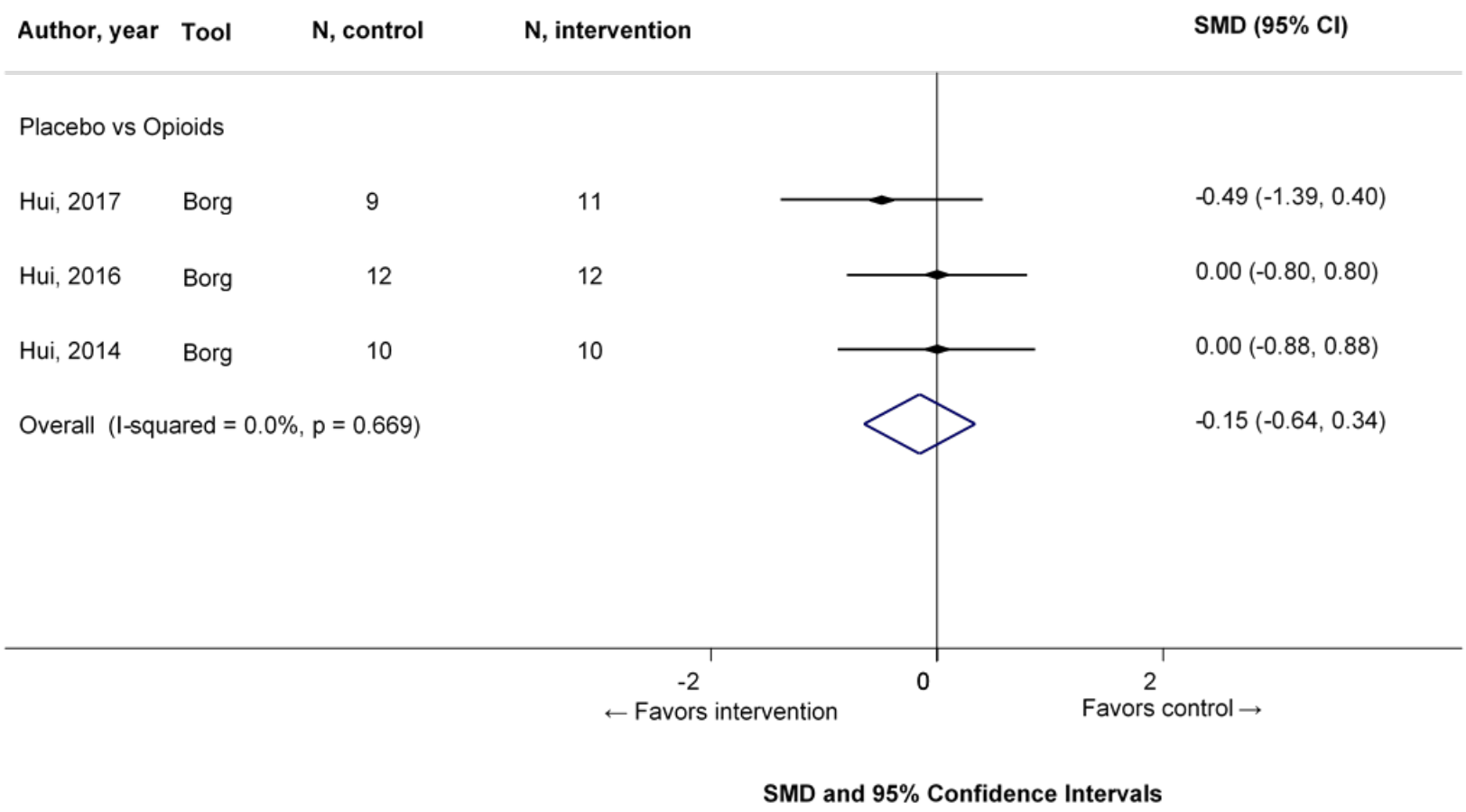
CI=confidence interval; N=sample size; NR=not reported; NRS=Numerical Rating Scale; RR=relative risk

eFigure 15. Meta-analysis of the effects of placebo vs opioids on drowsiness outcomes in patients with advanced cancer in inpatient hospice or palliative care units



CI=confidence interval; N=sample size; NR=not reported; NRS=Numerical Rating Scale; RR=relative risk

eFigure 16. Meta-analysis of the effects of placebo vs opioids on fatigue outcomes in patients with advanced cancer in inpatient hospice or palliative care units



CI=confidence interval; N=sample size; NR=not reported; SMD=standardized mean difference