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Efficacy and safety of systemic morphine for persistent breathlessness in adults with advanced nonmalignant disease: a systematic review and meta-analysis of randomized trials

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Abstract

Background. Morphine is used for persistent breathlessness despite uncertainty about its efficacy and safety in advanced nonmalignant diseases. We evaluated its symptomatic, functional, physiologic, and adverse effects.

Methods. We conducted a systematic review of randomized trials comparing systemic morphine with placebo or usual care in adults with persistent breathlessness due to advanced nonmalignant disease. We excluded acute or cancer-related breathlessness and non-systemic administration. PubMed, Embase, Scopus, and Web of Science were searched through July 2026. PRISMA 2020, RoB 2, and GRADE were applied. Random-effects meta-analyses used the Paule–Mandel estimator with Hartung–Knapp adjustment.

Results. Of 2,721 records, 15 reports representing 11 independent cohorts and 840 participants were included; five cohorts contributed to six meta-analyses. Compared with placebo, morphine probably results in little to no difference in worst daily-life breathlessness [mean difference (MD), −0.15; 95% confidence interval (CI), −0.63 to 0.34; moderate certainty] and may result in little to no difference in average breathlessness (MD, −0.09; 95% CI, −0.61 to 0.42; low certainty). Evidence for six-minute walk distance and respiratory rate was very uncertain. Changes in oxygen saturation and carbon dioxide tension were small and of low certainty. Several trials reported more adverse events or discontinuations with morphine, but heterogeneity in outcome measurement precluded pooling.

Conclusions. Short-term randomized evidence does not support expecting a clinically important benefit of regular oral morphine for daily-life breathlessness. Any therapeutic trial should be individualized, time limited, and closely monitored.

Keywords: dyspnea; morphine; analgesics, opioid; palliative care; systematic reviews as topic; randomized controlled trials as topic; meta-analysis as topic

Introduction

Chronic refractory breathlessness is characterized by persistent breathing difficulty at rest or during exertion, with functional limitation despite optimal treatment of the underlying disease [1, 2]. In advanced chronic obstructive pulmonary disease (COPD), its prevalence may reach 94% during the last year of life [1]. It is also common in other advanced nonmalignant diseases, including heart failure and interstitial lung diseases [3, 4]. In heart failure, mechanisms such as pulmonary congestion, hypoperfusion, and psychological distress may contribute to its persistence despite disease-directed treatment [4]. Chronic breathlessness limits exercise capacity and independence, promotes physical inactivity and social isolation, and impairs quality of life and psychological well-being [2, 3].

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After optimization of treatment for the underlying disease and nonpharmacologic interventions, some guidelines consider a carefully monitored trial of regular, low-dose oral opioids titrated to response in patients with severe refractory breathlessness; however, this recommendation is tentative, and the evidence remains limited and partly conflicting [5]. The biological rationale includes central modulation of breathlessness perception through opioid receptors, although some mechanistic evidence comes from experimental studies or studies of other opioids [2, 6]. In a small single-dose crossover trial in advanced COPD, immediate-release oral morphine reduced ventilation and respiratory rate during exercise at isotime and reduced exertional breathlessness; these acute findings do not by themselves establish sustained benefit in daily life [7]. Clinical barriers persist because of concerns about respiratory depression or hastening death and insufficient confidence or experience in prescribing these drugs [8]. Common adverse effects, including somnolence, nausea, vomiting, and constipation, must also be considered [6, 9].

Previous systematic reviews have rated the certainty of the evidence as low or very low, mainly because of small trials, risk of bias, inconsistency, and imprecision [5, 9]. Analytical decisions in earlier syntheses, including the handling of crossover designs and the use of fixed-effect models despite clinical and methodological heterogeneity, have also been questioned [6]. Combining malignant and nonmalignant diseases, different opioids, multiple routes of administration, and acute and scheduled regimens limits the direct applicability of those conclusions to regular oral morphine for chronic nonmalignant breathlessness [6, 9]. Individual studies range from single-dose exposures to brief courses, generally from several days to one to four weeks, and evidence on long-term benefits and harms remains limited [3, 6, 7]. A contemporary review that distinguished laboratory outcomes from symptoms in daily life found no clinically important improvement in daily-life breathlessness [10], and a subsequent phase 3 trial likewise found no reduction in worst breathlessness at 28 days [11]. Taken together, uncertainty remains regarding the magnitude, clinical relevance, and safety of morphine effects in this population.

We therefore conducted a systematic review and meta-analysis of randomized clinical trials to estimate the symptomatic, functional, physiologic, and safety effects of systemic morphine in adults with chronic breathlessness of nonmalignant origin. By identifying independent randomized cohorts, quantitatively synthesizing clinically comparable regimens and time points, analyzing distinct outcomes separately, and assessing risk of bias and certainty of evidence, we sought to clarify the magnitude, uncertainty, and applicability of the observed effects.

Methods

Protocol and registration

This systematic review and meta-analysis was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 [12], and the search was documented according to PRISMA-S [13]. The protocol was registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD420261468021). The flow diagram was created with the PRISMA2020 application [14].

Eligibility criteria

Randomized clinical trials (RCTs) with parallel-group, crossover, or dose-ranging designs were eligible if they enrolled adults (≥ 18 years) with persistent or refractory breathlessness due to advanced nonmalignant disease despite treatment of the underlying condition considered optimal by the study authors. Mixed populations were eligible only when data for the nonmalignant subgroup could be separated. We included systemic morphine administered orally or parenterally, at any dose and for any duration, compared with placebo, usual care, or no scheduled morphine. No restrictions were imposed by date, geographic location, or language.

We excluded studies of acute, postoperative, or procedure-related breathlessness; studies in which morphine was administered primarily for pain and breathlessness was not an objective; nebulized, inhaled, epidural, or intrathecal administration; multiple-opioid interventions when the effect of morphine could not be isolated; and studies without an eligible comparator.

Information sources and search strategy

PubMed, Embase, Scopus, and Web of Science Core Collection were searched from inception through July 2026. The strategies combined controlled vocabulary and free-text terms for four concepts: persistent or refractory breathlessness, systemic morphine, advanced nonmalignant disease, and clinical outcomes. Syntax was adapted for each platform. The complete search strategies are available in the PROSPERO record. Trial registries were not searched, and backward or forward citation tracking was not performed.

Study selection

All records were organized in a master Microsoft Excel workbook. Duplicates were removed by DOI or, when a DOI was unavailable, by matching title, author, and year. Two reviewers independently screened titles and abstracts, and potentially eligible records underwent full-text assessment. A reason was recorded for every full-text exclusion. Disagreements were resolved by consensus and, when necessary, consultation with a third reviewer.

Data collection process

Two reviewers extracted data using a standardized Microsoft Excel form. A third reviewer checked the extracted information against the full-text reports and resolved discrepancies. Missing information was recorded as not reported and was not imputed. Reports arising from the same cohort were linked as a study family using trial registration, authorship, sample, and intervention characteristics. No family contributed more than one estimate to the same synthesis; priority was given to the primary report or the report providing the most complete data for the outcome and time point of interest.

Data items and outcomes

We extracted bibliographic information; country and setting; design; inclusion criteria; sample size; demographic and clinical characteristics; underlying disease; definition of refractory breathlessness; intervention and comparator details (route, dose, formulation, frequency, and duration); co-interventions; funding; and conflicts of interest. For each outcome, we recorded its definition, instrument or unit, measurement time point, number analyzed, effect estimate, and measure of precision or variance.

The primary outcomes were average and worst breathlessness during daily life. They were retained as separate constructs and harmonized to a 0–10 numerical rating scale, for which negative mean differences favored morphine. Additional outcomes were six-minute walk distance (m), respiratory rate (breaths/min), resting peripheral oxygen saturation (percentage points), and carbon dioxide tension (kPa). Clinically distinct measurement time points were kept separate. Other prespecified outcomes that could not be pooled were described narratively.

Risk-of-bias assessment

Risk of bias was assessed for each numerical result with the Cochrane Risk of Bias 2 tool (RoB 2), targeting the effect of assignment to the intervention [15, 16]. Two reviewers independently answered the signaling questions and judged five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. A third reviewer resolved discrepancies. The overall judgment (low risk, some concerns, or high risk) was determined with the RoB 2 algorithm rather than solely by the worst domain. For crossover trials, sequence and period, washout, possible carryover, and use of paired analyses were also considered.

Effect measures and preparation of results

Mean differences with 95% confidence intervals (CIs) were used because each construct was reported in a common unit. When necessary, standard errors were reconstructed from 95% CIs. Carbon dioxide values reported in mmHg were converted to kPa using a factor of 0.133322. No other imputations were performed. In crossover trials, estimates without a recoverable paired variance were not analyzed as if they came from independent groups, and each participant was counted only once [15].

Statistical analysis

A meta-analysis was performed only when at least three independent study families reported the same outcome at comparable follow-up times. Each family contributed one morphine-versus-control comparison to each synthesis. Repeated assessments of oral morphine between 1 and 4 weeks were pooled only when the construct and follow-up were clinically comparable; acute exercise assessments were not combined with resting measurements. For the primary BEAMS syntheses, the 16 mg/day comparison was selected because it was more comparable with the 20 mg/day regimens in the other trials; the 8 mg/day comparison replaced, rather than supplemented, it in sensitivity analysis.

Analyses were conducted in R version 4.5.1 [17] with the meta version 8.2-1 and metafor version 4.8-0 packages [18, 19]. Inverse-variance random-effects models were fitted. Between-study variance (τ^2) was estimated with the Paule–Mandel method and its confidence interval (CI) with the Q-profile method [20].

The 95% CI for the pooled effect used the Hartung–Knapp adjustment with an ad hoc safeguard against a standard error smaller than the conventional estimate [21]. Prediction intervals were not calculated because all syntheses included fewer than five families.

Heterogeneity was described using I^2, τ^2, Cochran's Q test, and inspection of forest plots. I^2 values

< 30%, 30–60%, and > 60% were used as descriptive references for low, moderate, and high heterogeneity, respectively, rather than as rigid thresholds [22]. An I^2 of 0% was not interpreted as evidence of clinical homogeneity because few families were available. Sensitivity analyses repeated the models with conventional normal CIs and with restricted maximum likelihood and DerSimonian–Laird estimators; the primary dose was also replaced by the prespecified alternative comparison. Leave-one-out analysis was conducted only when at least three families remained after removal of one family. Prespecified subgroup analyses and meta-regression were not performed because few families contributed to each outcome. Post hoc exploratory analyses restricted to the three COPD cohorts were conducted for average and worst daily-life breathlessness using the same random-effects methods as the primary analyses.

Selection of the reported result within each study was assessed in RoB 2 domain 5. Publication bias and small-study effects were considered separately; funnel plots and asymmetry tests were not performed because each meta-analysis included only three or four families. The inability to assess these phenomena formally was not interpreted as evidence of their absence [15, 23].

Certainty of evidence was assessed by outcome using Grading of Recommendations Assessment, Development and Evaluation (GRADE) [23, 24]. Evidence from RCTs started at high certainty and could be downgraded for risk of bias, inconsistency, indirectness, imprecision, or publication bias. Prespecified clinical thresholds were used to interpret imprecision: ± 1.0 point on the 0–10 breathlessness scale [25], ± 30 m for six-minute walk distance [26], ± 2 breaths/min, ± 2 percentage points of oxygen saturation, and ± 0.5 kPa of carbon dioxide. The last three were treated as prespecified clinical thresholds rather than validated minimal clinically important differences. Certainty was rated high, moderate, low, or very low, and evidence profiles were prepared in GRADEpro GDT [27].

Results

Study selection

Database searches identified 2,721 records; 1,325 duplicates were removed. Of 1,396 screened records, 1,367 were excluded. Twenty-nine reports were sought, three were not retrieved, and 26 were assessed for eligibility. Eleven were excluded because of an ineligible population (n = 6), ineligible design or a nonmatching full text (n = 2), no eligible outcome (n = 1), no eligible comparator (n = 1), or a secondary/duplicate publication (n = 1). Fifteen reports representing 11 independent randomized cohorts were included [7, 28–41] (Figure 1).

Characteristics of included cohorts

The 11 cohorts randomized 840 participants; mean or median age ranged from 63.6 to 75.5 years, and 309/816 participants with reported sex were women (37.9%). Six used crossover and five parallel-group designs. Four cohorts enrolled patients with COPD, three with chronic heart failure, one with fibrotic interstitial lung disease, one with pulmonary arterial hypertension, and two with mixed causes of chronic breathlessness (Table 1).

Intervention and outcome characteristics

All cohorts evaluated oral morphine. Repeated regimens were usually 20 mg/day; BEAMS tested initial doses of 8 and 16 mg/day with subsequent blinded titration [38], whereas Abdallah et al. administered a single 0.1 mg/kg dose [7]. All eligible comparisons used matched placebo; two multiarm crossover trials also included transdermal fentanyl [28] or oral oxycodone [34]. Randomized periods ranged from one dose to 12 weeks, with reported crossover washouts of 2–7 days. Daily-life breathlessness was measured with a 0–10 numerical rating scale in five cohorts, a visual analog scale in five, and the modified Borg scale in one. Secondary reports [29, 39, 41] and one pooled analysis [33] added no independent cohort.

Effects of systemic morphine

Compared with placebo, morphine may result in little to no difference in average daily-life breathlessness [mean difference (MD), −0.09 points; 95% CI, −0.61 to 0.42; four cohorts; low certainty; Figure 2A and Table 2] and probably results in little to no difference in worst daily-life breathlessness (MD, −0.15; 95% CI, −0.63 to 0.34; four cohorts; moderate certainty; Figure 2B and Table 2). Both CIs remained within the prespecified ± 1-point threshold. In *post hoc* analyses restricted to the three COPD cohorts, the pooled estimates were similar for average daily-life breathlessness (MD, −0.12; 95% CI, −0.85 to 0.60; I^2 = 0%) and worst daily-life breathlessness (MD, −0.17; 95% CI, −0.84 to 0.51; I^2 = 0%) (Figure 2A, B). Morphine may result in little to no difference in resting pulse oxygen saturation (MD, −0.39 percentage points; 95% CI, −1.57 to 0.78) or blood carbon dioxide tension (MD, 0.13 kPa; 95% CI, −0.14 to 0.41; three cohorts each; low certainty; Figure 3B, C and Table 2); both CIs remained within their prespecified thresholds. Evidence for six-minute walk distance (MD, 4.94 m; 95% CI, −36.85 to 46.72; Figure 2C) and resting respiratory

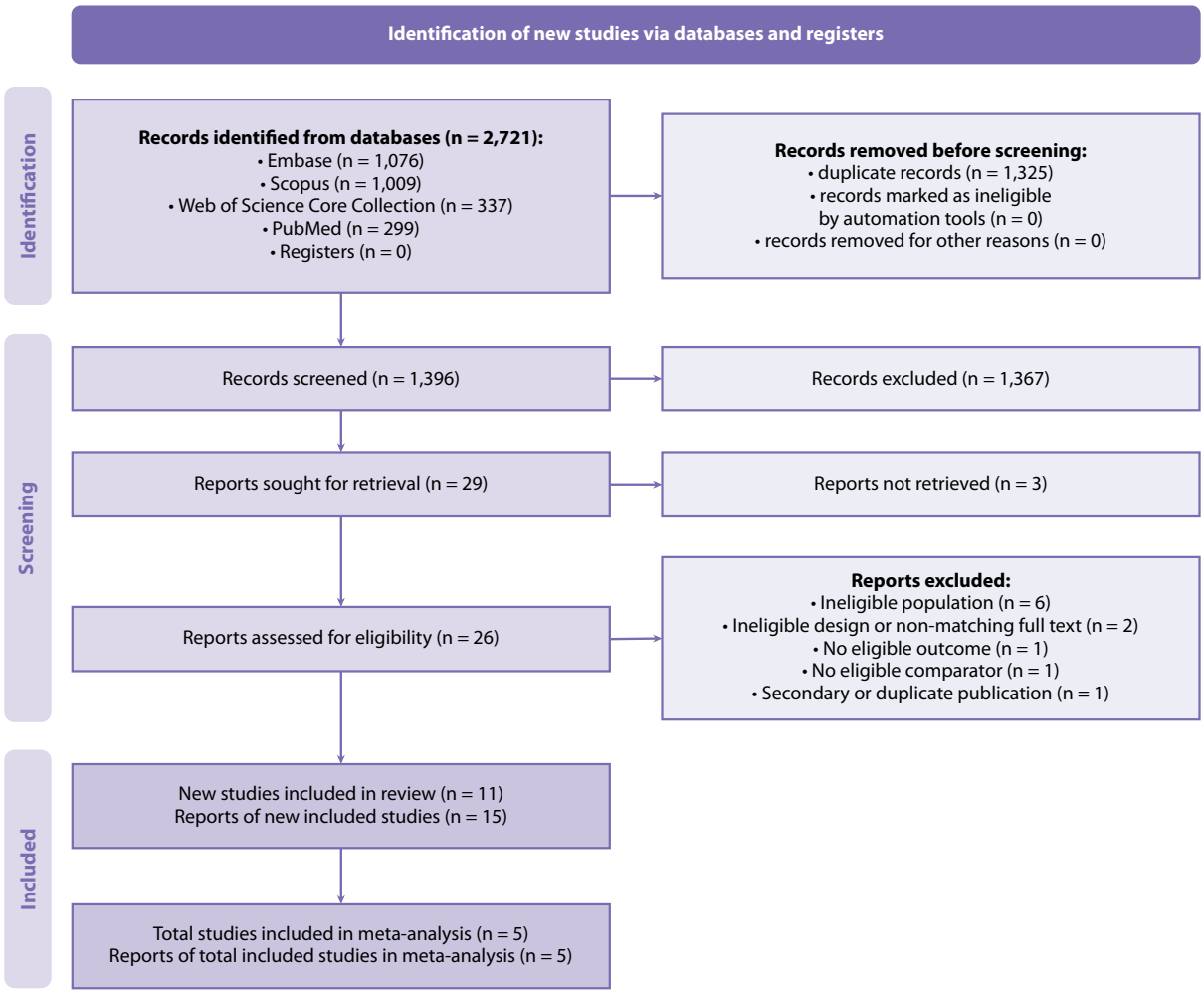


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram of study identification, screening, eligibility and inclusion; The diagram was generated with the PRISMA2020 Shiny application [14]. Database totals correspond to captured records. Five independent cohorts contributed to at least one meta-analysis

rate (MD, −1.76 breaths/min; 95% CI, −4.29 to 0.77; Figure 3A) was very uncertain (three cohorts each; Table 2). None of the six pooled 95% CIs excluded the null.

Safety and tolerability

Safety outcomes were not pooled because definitions, exposure periods, and paired discordant counts differed. In MoreFoRCOPD, adverse events occurred in 22/46 participants during morphine and 24/44 during placebo; vomiting occurred in 5/45 versus 0/44 [28]. In week 1 of BEAMS, treatment-emergent adverse events occurred in 35/55 participants receiving 8 mg, 40/51 receiving 16 mg, and 24/50 receiving placebo; discontinuations were 2/55, 5/51, and 0/50 [29, 38]. In MORDYC, opioid-related adverse effects occurred in 43/53 morphine and 40/57 placebo participants [30]. In MORPH-ILD, constipation, nausea, and confusion occurred in 7/18 versus 2/18, 8/18 versus 4/18, and 7/18 versus 2/18, respectively [31]. In Breathe MOR-HF, new or worsened grade ≤ 2 events occurred in 17/21 versus 6/24, treatment withdrawals in 11/21 versus 5/24, and serious adverse events in 12 versus 15 participants over 12 weeks [32]. Other brief trials reported more constipation, nausea, or withdrawals with morphine [34, 36, 37]; one severe hypersensitivity event occurred in the acute Abdallah trial [7]. BEAMS secondary analyses found no worsening of daytime sleepiness [39] or overall withdrawal scores, although two participants had severe scores during the three assessed days [41].

Risk of bias across trials

Of 94 outcome-level RoB 2 assessments, 86 (91.5%) were high risk, six (6.4%) raised some concerns, and two (2.1%) were low risk. Selection of the reported

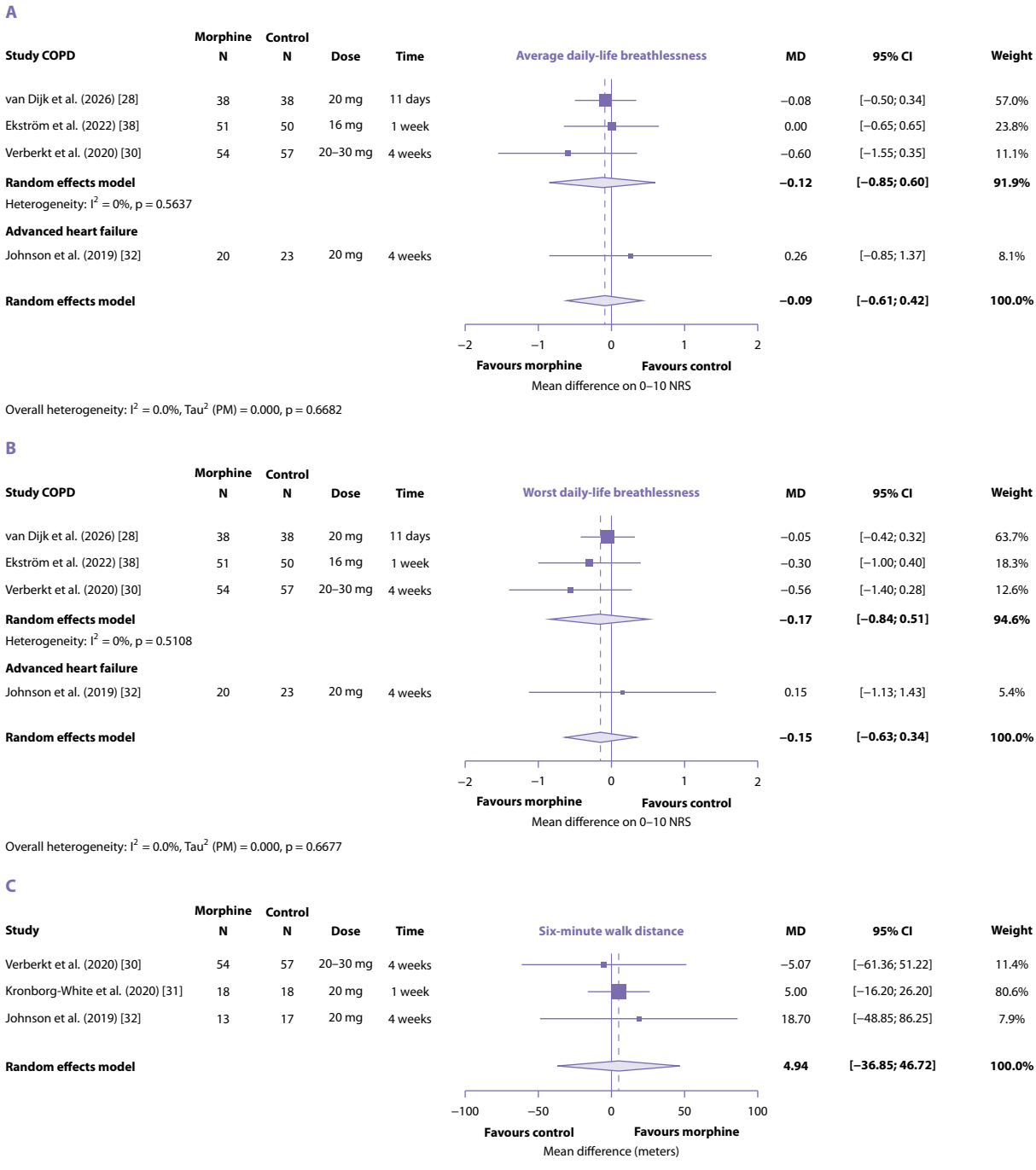


Figure 2. Effects of morphine versus placebo on daily-life breathlessness and functional capacity; Panels: **A** — average daily-life breathlessness; **B** — worst daily-life breathlessness; **C** — six-minute walk distance. Squares are cohort estimates and diamonds are pooled estimates. In crossover trials, morphine and control N values represent the same participants observed in both periods. In panels **A** and **B**, *post hoc* COPD-restricted pooled estimates are shown alongside the overall estimates. No formal test for subgroup differences was performed because only one heart-failure cohort was available. A COPD-restricted synthesis was not performed for panel C because only one COPD cohort contributed to that outcome; MD — mean difference; NRS — numerical rating scale; PM — Paule–Mandel

Table 1. Study, intervention, comparator and outcome-assessment characteristics of included randomized trial cohorts

Study or trial	Cohort and design	Morphine intervention	Comparator, treatment and washout	Main outcome assessment
van Dijk et al., 2026 (MoreFoRCOPD) [28]	N = 58; COPD GOLD III–IV; Netherlands; 3-period crossover	Oral sustained-release morphine 10 mg twice daily (20 mg/day)	Matched double-dummy placebo; transdermal fentanyl 12 µg/h as third arm; 11-day periods; 3-day washout	Mean and worst daily-life breathlessness, 0–10 NRS; end of each 11-day period
Ekström et al., 2022 (BEAMS) [38]	N = 160; COPD; Australia; parallel dose-ranging trial	Oral extended-release morphine 8 or 16 mg once daily in week 1; blinded titration to 24–32 mg/day	Matched placebo once daily; three blinded weekly phases	Worst and average breathlessness, 0–10 NRS; week 1
Verberkt et al., 2020 (MORDYC) [30]	N = 124; COPD; Netherlands; parallel trial	Oral sustained-release morphine 10 mg twice daily, optionally three times daily (20–30 mg/day)	Matched placebo on the same schedule; 4 weeks	Daily-life breathlessness, 6MWD and resting physiology; week 4
Kronborg-White et al., 2020 (MORPH-ILD) [31]	N = 36; fibrotic ILD; Denmark; parallel trial	Oral morphine drops 5 mg four times daily (20 mg/day)	Matched placebo four times daily; 7 days	Past-week breathlessness, 6MWD and resting physiology; day 7
Johnson et al., 2019 (BreatheMOR-HF) [32]	N = 45; chronic heart failure; UK; parallel phase III trial	Oral modified-release morphine 10 mg twice daily (20 mg/day)	Matched placebo twice daily; 12 weeks; primary endpoint at week 4	Average and worst breathlessness, 6MWD and resting SpO_2; week 4
Oxberry et al., 2011 [34]	N = 39; chronic heart failure; UK; 3-period crossover	Oral morphine solution 5 mg four times daily (20 mg/day)	Matched placebo; oral oxycodone 2.5 mg four times daily as third arm; 4-day periods; 3-day washout	Breathlessness intensity, 100-mm VAS; day 4; no recoverable paired variance
Currow et al., 2007 (Abernethy cohort) [35]	N = 38; refractory breathlessness, mainly COPD; Australia; crossover	Oral sustained-release morphine 20 mg once daily	Matched placebo once daily; 4-day periods; washout not reported	Morning/evening breathlessness, 100-mm VAS; parent efficacy report unavailable
Johnson et al., 2002 [36]	N = 10; chronic heart failure; UK; crossover pilot	Oral morphine solution 5 mg four times daily (20 mg/day)	Matched placebo four times daily; 4-day periods; 2-day washout	Breathlessness intensity, 100-mm VAS; day 4; no direct paired effect
Ferreira et al., 2018 (PAH) [37]	N = 23; pulmonary arterial hypertension; Australia; crossover	Oral extended-release morphine 20 mg once daily	Matched placebo once daily; 7-day periods; 7-day washout	Current and daily-life breathlessness, 100-mm VAS; days 5–7; paired variance unavailable
Abdallah et al., 2017 [7]	N = 23 randomized; advanced COPD; Canada; acute crossover	Single oral immediate-release morphine dose, 0.1 mg/kg (maximum 10 mg)	Matched single-dose placebo; single-dose visits; > 48-hour washout	Exertional breathlessness, modified Borg scale; exercise isotime
Ferreira et al., 2024 [40]	N = 284; chronic breathlessness; Australia; parallel secondary analysis	Oral sustained-release morphine 20 mg once daily	Matched placebo once daily; 7 days	Five breathlessness VAS measures; days 5–7; no overall continuous primary effect

Rows represent 11 independent randomized cohorts rather than 15 publications. Secondary BEAMS reports [29, 39, 41] and the pooled preference analysis [33] were linked to their source cohorts. In crossover trials, morphine and control counts refer to the same participants and must not be added as independent observations; 6MWD — six-minute walk distance; COPD — chronic obstructive pulmonary disease; ILD — interstitial lung disease; NRS — numerical rating scale; PAH — pulmonary arterial hypertension; SpO_2 — peripheral oxygen saturation; VAS — visual analog scale

result was high risk in 84 assessments (89.4%), followed by missing outcome data (24; 25.5%), deviations from intended interventions (12; 12.8%), and outcome measurement (two; 2.1%); none was high risk for the randomization process (Figure 4). Of 20 estimates in the six meta-analyses, 17 were high risk, one raised some concerns, and two were low risk. Excluding high-risk estimates left fewer than two eligible estimates per synthesis, so the restricted sensitivity meta-analysis was not estimable.

Sensitivity analyses

Restricted maximum likelihood and DerSimonian–Laird models with Hartung–Knapp intervals and the standard-error safeguard reproduced the primary estimates because τ^2 was 0 in every synthesis. Replacing the 16 mg BEAMS comparison with 8 mg yielded MDs of −0.11 (95% CI, −0.62 to 0.39) for average breathlessness, −0.15 (−0.63 to 0.33) for worst breathlessness, −1.61 breaths/min (−4.13 to 0.91) for respiratory rate, and −0.37 percentage points (−1.54 to 0.80) for oxygen saturation; this substitution did not apply to walking distance or carbon dioxide tension. Leave-one-out analyses were possible only for the two breathlessness outcomes. Average-breathlessness MDs ranged from −0.12 to −0.03 (overall CI-limit range, −1.17 to 0.95), and worst-breathlessness MDs from −0.32 to −0.09 (−1.41 to 0.77); all CIs included the null. Conventional normal 95% CIs excluded the null for respiratory rate (−2.91 to −0.61) and carbon dioxide tension (0.01 to 0.26), whereas primary Hartung–Knapp CIs did not. Upper 95% CI limits for I^2 were 84.7% with four cohorts and 89.6% with three. Apart from the *post hoc* COPD-restricted analyses shown in Figure 2A, B, subgroup analyses, meta-regression, prediction intervals, funnel plots, and asymmetry

Table 2. Summary of findings for systemic morphine versus placebo in adults with persistent breathlessness

Outcome	Participants (cohorts); follow-up	Certainty (GRADE)	Absolute effect: MD (95% CI)	Interpretation
Average daily-life breathlessness (0–10 NRS)	293 (4); 11 days to 4 weeks	⊕⊕◯◯ Low[a]	0.09 points lower (0.61 lower to 0.42 higher)	May result in little to no difference
Worst daily-life breathlessness (0–10 NRS)	293 (4); 1 to 4 weeks	⊕⊕⊕◯ Moderate[b]	0.15 points lower (0.63 lower to 0.34 higher)	Probably results in little to no difference
Six-minute walk distance (m)	177 (3); 1 to 4 weeks	⊕◯◯◯ Very low[c, d]	4.94 m higher (36.85 lower to 46.72 higher)	Evidence is very uncertain
Resting respiratory rate (breaths/min)	248 (3); 1 to 4 weeks	⊕◯◯◯ Very low[c, e]	1.76 breaths/min lower (4.29 lower to 0.77 higher)	Evidence is very uncertain
Resting pulse oxygen saturation (percentage points)	241 (3); 1 to 4 weeks	⊕⊕◯◯ Low[c]	0.39 points lower (1.57 lower to 0.78 higher)	May result in little to no difference
Blood carbon dioxide tension (kPa)	180 (3); 11 days to 4 weeks	⊕⊕◯◯ Low[f]	0.13 kPa higher (0.14 lower to 0.41 higher)	May result in little to no difference

GRADE Working Group certainty: high, very confident that the true effect is close to the estimate; moderate, moderately confident; low, limited confidence; very low, very little confidence. Estimates used inverse-variance random-effects models with Paule–Mandel τ^2 and Hartung–Knapp confidence intervals with an *ad hoc* standard-error safeguard. No outcome was downgraded for inconsistency (I^2 = 0% in all six syntheses), indirectness, or publication bias. [a]downgraded two levels for risk of bias: 91.9% of the weight came from high-risk results and the analysis restricted to non-high-risk results was not estimable; [b]downgraded one level for risk of bias: 81.7% of the weight came from high-risk results and 18.3% from low-risk evidence. [c]downgraded two levels for risk of bias: all three estimates were high risk and the restricted analysis was not estimable; [d]downgraded two levels for very serious imprecision because the 95% CI crossed clinically important benefit and harm beyond ± 30 m; [e]downgraded one level for serious imprecision because the 95% CI crossed the null and –2 breaths/min. [f]downgraded two levels for risk of bias: 94.2% of the weight came from high-risk results and the remainder raised some concerns; CI — confidence interval; GRADE — Grading of Recommendations Assessment, Development and Evaluation; MD — mean difference; NRS — numerical rating scale; RoB 2 — Cochrane Risk of Bias 2

tests were not performed because too few cohorts were available.

Discussion

Principal findings

Five of the 11 independent randomized cohorts contributed to six meta-analyses. Regular low-dose oral morphine probably results in little to no clinically important difference in worst daily-life breathlessness between 7 days and 4 weeks (MD, –0.15 points; 95% CI, –0.63 to 0.34; moderate certainty) and may result in little to no difference in average breathlessness (MD, –0.09; 95% CI, –0.61 to 0.42; low certainty). Both intervals remained within the one-point threshold. Evidence for walking distance and respiratory rate was very uncertain, whereas changes in oxygen saturation and carbon dioxide tension were small and of low certainty. These short-term findings neither establish equivalence nor demonstrate safety.

Interpretation in the context of available evidence

Our findings are consistent with the review underpinning the European Respiratory Society program, which separated standardized measurements during exercise from those obtained in daily life: it identified benefit under laboratory conditions but not in daily life (standardized mean difference, –0.1; 95% CI, –0.64 to 0.44) [10]. Overlap of included trials makes this comparison a triangulation rather than an independent replication. That review found considerable heterogeneity in some analyses, whereas I^2 was 0% in ours; this difference may reflect narrower criteria and the use of common scales, but true heterogeneity cannot be excluded with only three or four cohorts. As external evidence excluded from the present synthesis because it involved a mixed population, the phase 3 MABEL trial of 140 participants likewise found no difference in worst breathlessness at day 28 (adjusted MD, 0.09; 95% CI, –0.57 to 0.75) [11].

External evidence for functional capacity is also inconclusive. The Cochrane review reported conflicting results and, for change from baseline, a 47.78 m difference favoring placebo (95% CI, 35.88 to 59.67); however, this estimate came from only two trials and 26 participants, with high heterogeneity (I^2 = 88%) and very low-certainty evidence [9]. The 30 m threshold used here is consistent with a pilot study that estimated a minimal clinically important difference of 30.1 m and a minimal detectable difference of 32.4 m [26]. A heart failure-specific synthesis found no clear benefit of opioids for breathlessness and more nausea, vomiting, constipation, and withdrawals [42]. A review of respiratory effects likewise reported small mean physiologic changes but emphasized heterogeneity and low study quality [43]. These comparisons support a cautious interpretation.

Safety beyond mean physiologic changes

Several included trials reported more adverse events, opioid-related symptoms, or discontinuations during morphine exposure, although the pattern was not uniform and follow-up ranged from one dose to 12 weeks [7, 28–32, 34, 36–39, 41]. Variation in definitions and denominators precluded a reliable pooled estimate. MABEL also reported more adverse events, serious events, and withdrawals with morphine, although no treatment–related deaths occurred [11]. Observational evidence is discordant:

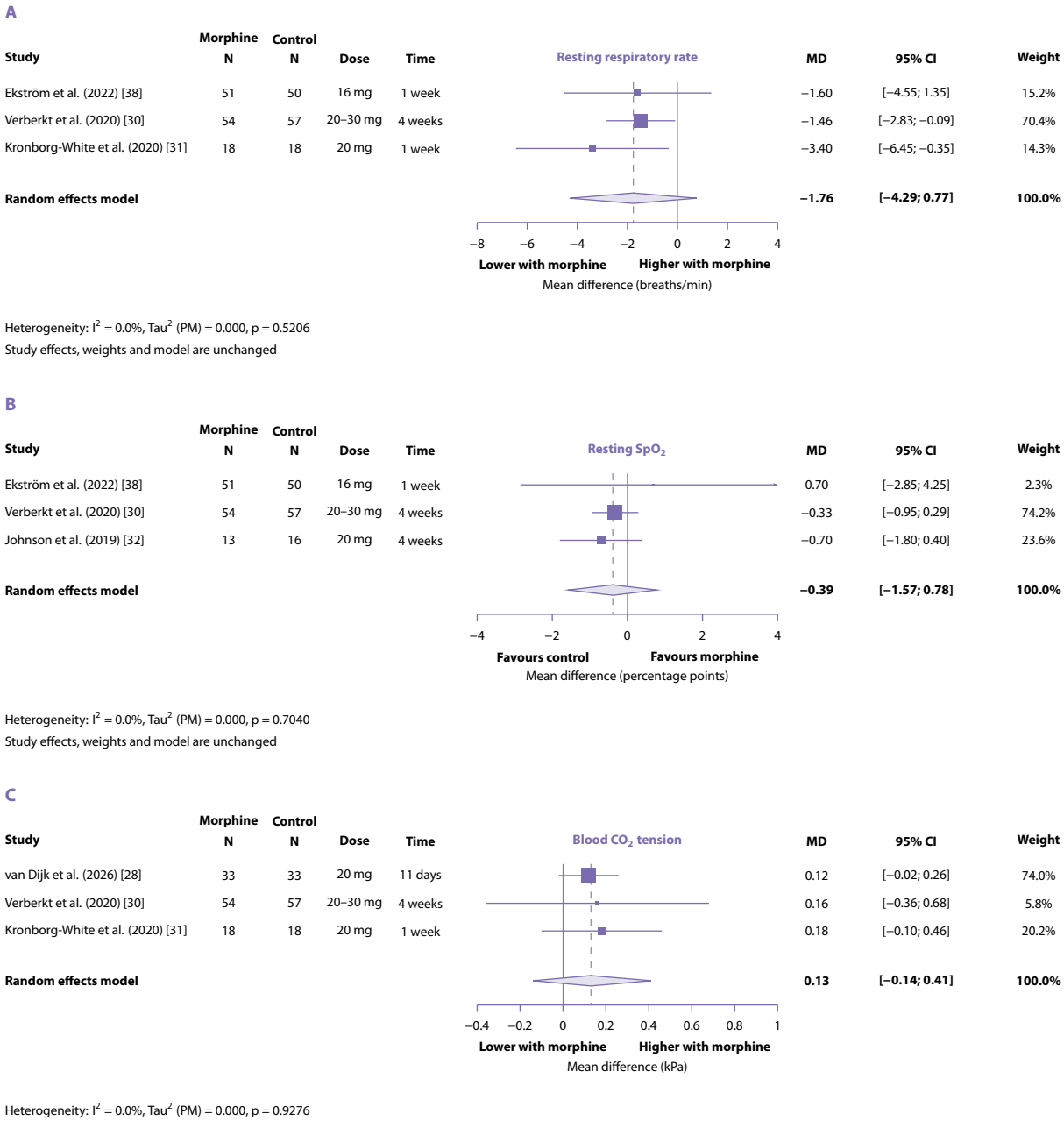


Figure 3. Effects of morphine versus placebo on respiratory physiology; Panels: **A** — resting respiratory rate; **B** — resting pulse oxygen saturation; **C** — blood carbon dioxide tension. Squares are cohort estimates and diamonds are pooled estimates. In crossover trials, morphine and control N values represent the same participants observed in both periods; MD — mean difference; PM — Paule–Mandel

among patients with very severe COPD, doses up to 30 mg/day of oral morphine equivalents were not associated with higher mortality, unlike higher doses [44], whereas incident dispensing of different opioids in older adults with COPD was associated with higher respiratory and all-cause mortality [45]. These associations do not establish causality, may reflect confounding by indication, and do not specifically evaluate the morphine regimen in this review; nonetheless, they reinforce that the absence of a mean physiologic change does not imply individual safety.

Limitations of the evidence

Of the 20 estimates included in meta-analyses, 17 were at high risk of bias, mainly because of selection of the reported result, and the planned analysis excluding high-risk results could not be estimated. Imprecision was very serious for walking distance and

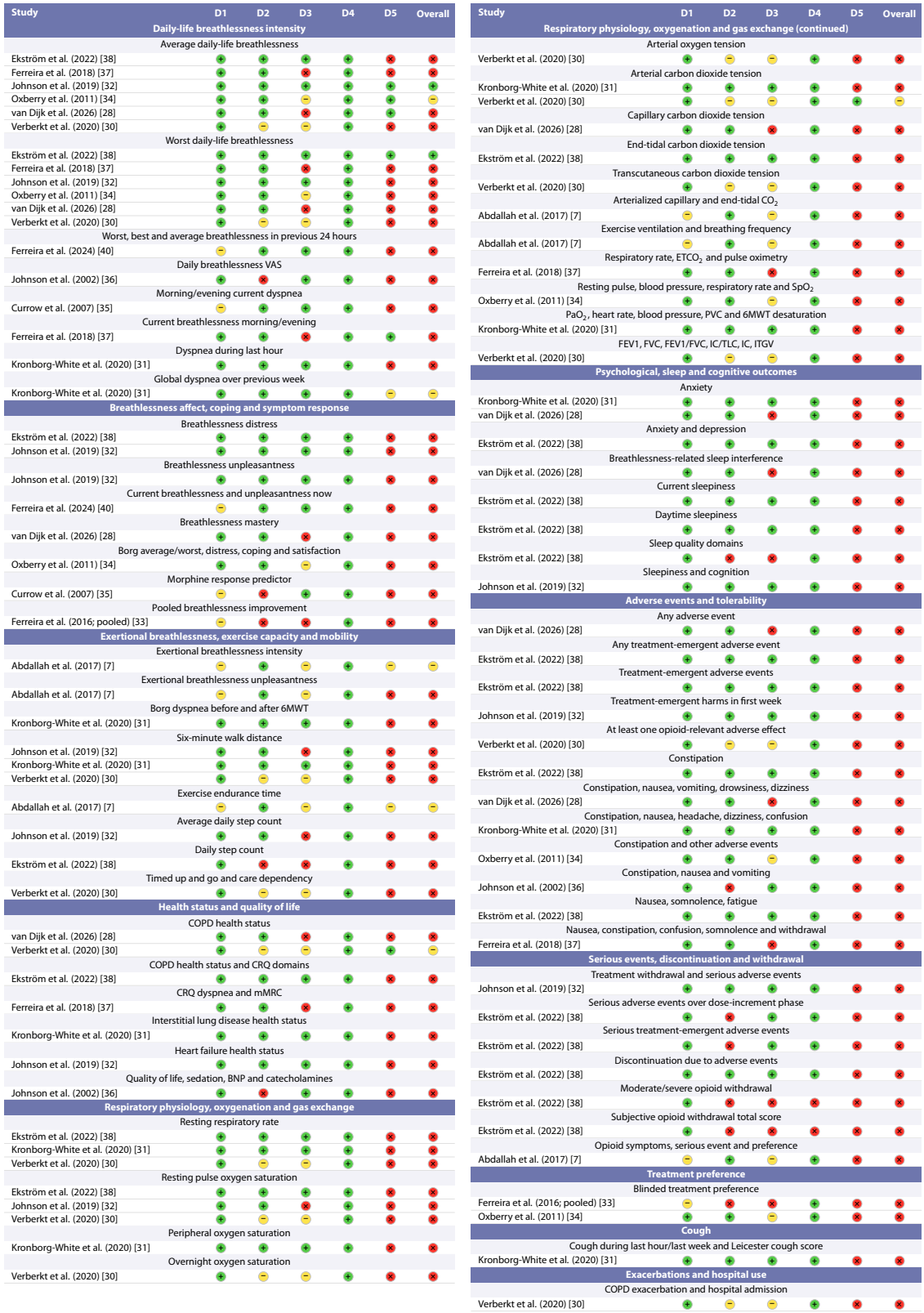


Figure 4. Risk of bias by specific outcome across all included randomized cohorts; The Figure presents all 94 result-level RoB 2 assessments across 73 outcomes. Green with plus sign, low risk; yellow with minus sign, some concerns; red with cross, high risk. D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result

serious for respiratory rate. Although I^2 was 0%, the upper limits of its CIs reached 84.7–89.6%, so important heterogeneity cannot be excluded. Conventional normal intervals excluded the null for respiratory rate and carbon dioxide tension, whereas the conservative Hartung–Knapp intervals included it; these signals were therefore not robust to the inferential method. Publication bias could not be assessed and should not be interpreted as absent.

Strengths and limitations of the review process

Strengths include reconstruction by cohort to avoid double counting, outcome-specific risk-of-bias judgments, use of mean differences on common scales, and Hartung–Knapp inference. However, only five cohorts contributed quantitatively, so estimates rest on a narrower evidence base than the full set of included studies; three full-text reports could not be retrieved; safety outcomes required narrative synthesis; and the small number of studies precluded reliable between-disease subgroup comparisons, meta-regression, prediction intervals, and evaluation of small-study effects. The COPD-restricted analyses were post hoc and included only three cohorts.

Implications for practice and policy

Guidelines make different recommendations from very low-certainty evidence. The 2024 European Respiratory Society guideline suggests not using opioids in people with serious respiratory illness [46], whereas the 2020 American Thoracic Society guideline made a conditional recommendation to consider opioid-based treatment in patients with COPD and advanced refractory breathlessness despite optimal therapy [47]. Our findings argue against routine prescribing when an average benefit is expected but do not show that no individual can respond. A 2023 narrative review found no consistent evidence of a responder phenotype by disease or severity [48]; nonrandomized studies reporting approximately 60% responders lack placebo controls and are vulnerable to confounding and expectation bias [49]. The quantitative syntheses apply mainly to scheduled oral morphine doses of 16–30 mg/day for 7 days to 4 weeks, predominantly in COPD, with one cohort each in heart failure and fibrotic interstitial lung disease. They should not be extrapolated to higher doses, other opioids, parenteral administration, rescue-only use, or end-of-life care.

Implications for research

Adequately powered parallel-group trials with standardized oral regimens, prespecified analyses, and longer follow-up are needed. Harmonized definitions of serious adverse events, withdrawal because of adverse events, and post-discontinuation symptoms would permit the synthesis that was not possible here. Validated response thresholds are also needed for physiologic variables. An individual participant data meta-analysis could assess whether disease, baseline severity, or early response identifies subgroups with a favorable benefit-harm balance.

Conclusions

Short-term randomized evidence does not support expecting a clinically important improvement in daily-life breathlessness or walking capacity with regular low-dose oral morphine. Certainty ranged from moderate to very low, and the predominance of high-risk-of-bias results precludes conclusions of equivalence or definitive safety. Morphine should therefore not be prescribed routinely with the expectation of an average benefit. If an individual therapeutic trial is considered after optimization of disease-directed treatment and nonpharmacologic measures, it should be based on shared decision-making, be time limited, and include close monitoring of symptomatic response and adverse effects.

Article information and declarations

Role of artificial intelligence in creating content

During the preparation of this work, the authors used ChatGPT (GPT-5.6 SoI; OpenAI) for translation assistance and language/style refinement. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Author contributions

RVBR: conceptualization, data curation, formal analysis, investigation, methodology, validation, writing — original draft, writing — review and editing; AERC: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, writing — original draft, writing — review and editing; RMPS: conceptualization, data curation, formal analysis, investigation, methodology, validation, writing — original draft, writing — review and editing. All authors critically reviewed and approved the final version of the manuscript and agree to be accountable for the work.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Supplementary material

None.

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