

Interventions to prevent and reduce physician burnout: a systematic review and meta-analysis



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Summary

Background Physician burnout has reached epidemic levels, as documented in national studies of both physicians in training and practising physicians. The consequences are negative effects on patient care, professionalism, physicians' own care and safety, and the viability of health-care systems. A more complete understanding than at present of the quality and outcomes of the literature on approaches to prevent and reduce burnout is necessary.

Methods In this systematic review and meta-analysis, we searched MEDLINE, Embase, PsycINFO, Scopus, Web of Science, and the Education Resources Information Center from inception to Jan 15, 2016, for studies of interventions to prevent and reduce physician burnout, including single-arm pre-post comparison studies. We required studies to provide physician-specific burnout data using burnout measures with validity support from commonly accepted sources of evidence. We excluded studies of medical students and non-physician health-care providers. We considered potential eligibility of the abstracts and extracted data from eligible studies using a standardised form. Outcomes were changes in overall burnout, emotional exhaustion score (and high emotional exhaustion), and depersonalisation score (and high depersonalisation). We used random-effects models to calculate pooled mean difference estimates for changes in each outcome.

Findings We identified 2617 articles, of which 15 randomised trials including 716 physicians and 37 cohort studies including 2914 physicians met inclusion criteria. Overall burnout decreased from 54% to 44% (difference 10% [95% CI 5–14]; $p < 0.0001$; $I^2 = 15\%$; 14 studies), emotional exhaustion score decreased from 23.82 points to 21.17 points (2.65 points [1.67–3.64]; $p < 0.0001$; $I^2 = 82\%$; 40 studies), and depersonalisation score decreased from 9.05 to 8.41 (0.64 points [0.15–1.14]; $p = 0.01$; $I^2 = 58\%$; 36 studies). High emotional exhaustion decreased from 38% to 24% (14% [11–18]; $p < 0.0001$; $I^2 = 0\%$; 21 studies) and high depersonalisation decreased from 38% to 34% (4% [0–8]; $p = 0.04$; $I^2 = 0\%$; 16 studies).

Interpretation The literature indicates that both individual-focused and structural or organisational strategies can result in clinically meaningful reductions in burnout among physicians. Further research is needed to establish which interventions are most effective in specific populations, as well as how individual and organisational solutions might be combined to deliver even greater improvements in physician wellbeing than those achieved with individual solutions.

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Introduction

Physician burnout, a work-related syndrome involving emotional exhaustion, depersonalisation, and a sense of reduced personal accomplishment,¹ has reached epidemic levels, with prevalences near or exceeding 50%, as documented in national studies of both physicians in training^{2,3} and practising physicians.^{4–6} Consequences are negative effects on patient care,^{7–9} professionalism,^{10,11} physicians' own care and safety (including diverse issues such as mental health concerns and motor vehicle crashes),^{12,13} and the viability of health-care systems, including reductions in physicians' professional work effort.^{14,15} Evidence has linked 1 point changes in burnout scores with meaningful differences in self-perceived major medical errors,^{8,9} reductions in work hours,¹⁵ and suicidal ideation.¹² These concerns have prompted calls for increased attention to physician wellbeing, including efforts targeting burnout.^{16–18} Both individual-focused and structural or organisational solutions are required.¹⁶

A more complete understanding than at present of the quality and outcomes of the literature on approaches to prevent and reduce burnout is necessary to understand the best evidence for effective interventions and to establish a strong foundation for further research to fill gaps in this literature.

Previous reviews of physician distress have been limited in their ability to inform these issues by a combination of factors, such as an absence of focus on physicians and burnout and inconsistent adherence to modern methodological systematic review standards.^{19–22} Therefore, we did a systematic review and meta-analysis adhering to methodological standards to examine the literature to date on interventions to prevent and reduce physician burnout.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis (reported according to the Preferred Reporting Items for Systematic

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Research in context

Evidence before this study

We searched MEDLINE, Embase, and PsycINFO from inception to Jan 15, 2016, for previously published systematic reviews and meta-analyses on interventions to prevent and reduce physician burnout, using search terms including “burnout” and “stress”, with no language restrictions. Previous reviews were limited by an absence of focus on physicians or burnout and inconsistent adherence to modern methodological systematic review standards.

Added value of this study

Our study provides the most comprehensive systematic review and meta-analysis to date of all studies assessing the effect of interventions on burnout among physicians, summarising results of 15 randomised controlled trials and 37 observational studies. Our findings emphasise that many individual-focused and organisational interventions offer meaningful benefit in combating physician burnout. Effective individual-focused strategies include mindfulness-based approaches, stress

management training, and small group curricula. Effective organisational approaches include duty hour requirements and locally developed modifications to clinical work processes.

Implications of all the available evidence

Our results substantiate that individual-focused interventions, such as mindfulness, stress management, and small group discussions, and structural or organisational interventions can be effective approaches to reduce burnout domain scores. Duty hour limitation policies appear effective, although, at present, these results are derived only from observational studies in the USA. The effect of individual-focused and structural or organisational approaches in combination has not been studied, and which classes of interventions might be most effective for specific groups of physicians remains unknown. Additionally, further research is needed to clarify optimal approaches to development and implementation of interventions. Finally, sustainability of intervention effects is poorly understood as few studies have assessed long-term burnout outcomes.

Reviews and Meta-Analyses statement²³), we did a literature search to identify studies of interventions to prevent and reduce physician burnout, with the aid of an experienced medical librarian (PJE). We included studies collecting comparative data to assess the effect of an intervention on physician burnout, excluding studies of medical students and non-physician health-care providers. We included single-arm pre-post comparison studies. We required studies to provide physician-specific burnout data using burnout measures with validity support from commonly accepted sources of evidence, consisting of the domains of content, response process, internal structure, relations to other variables, and consequences.²⁴

We searched MEDLINE, Embase, PsycINFO, Scopus, Web of Science, and the Education Resources Information Center from inception to Jan 15, 2016. Search terms included “burnout” and “stress”, along with numerous other wellbeing-related terms. We applied no language restrictions. The full search strategies are detailed in the appendix. We also reviewed the reference lists of eligible studies and previous evidence summaries to identify additional literature.

Two reviewers (CPW and LND or CPW and TDS) working independently considered the potential eligibility of each of the abstracts generated by the search strategy. Full-text articles were obtained unless both reviewers decided that an abstract was ineligible. Each full-text report was assessed independently for final study inclusion. Disagreements about inclusion of full-text articles were resolved by consensus and we measured agreement on inclusion of full-text articles with the κ statistic.

Data analysis

We extracted data using a standardised form to enter intervention descriptions, study participant characteristics, study design, and study results according to the burnout metric applied in each study. Outcomes were differences between intervention groups in overall burnout, emotional exhaustion score (and high emotional exhaustion), and depersonalisation score (and high depersonalisation). We extracted the SE of each outcome measure directly or calculated it from relevant reported statistical results, such as *p* values and CIs. Data extraction was assessed by two reviewers (CPW and LND or CPW and TDS), and disagreements were resolved by consensus. We contacted authors of studies to obtain missing data. Duplicate data were not an issue because we specified the timepoint closest to the conclusion of the intervention for each study, so multiple reports from the same cohort were never included in the same analysis.

We used random-effects models to calculate pooled mean differences using the generic inverse variance method to incorporate heterogeneity related to different interventions, settings, study designs, and burnout metrics across studies. We scaled individual burnout domain scores to the relevant full Maslach Burnout Inventory range (0–54 for emotional exhaustion score and 0–30 for depersonalisation score).¹ When not reported, we calculated SEs from available data.

Risk of bias was assessed by two reviewers (CPW and LND or CPW and TDS) using Cochrane Collaboration risk assessment tools for both randomised and observational study designs.^{25,26} Disagreements were resolved by consensus. We measured heterogeneity using *I*². To explore sources of heterogeneity, we prespecified subgroup

See Online for appendix

analyses, consisting of comparisons of individual-focused versus structural or organisational interventions, studies of residents versus practising physicians, and different study designs (randomised controlled trials vs observational studies). Variability within studies is reported in the forest plots and incorporated into the standard meta-analysis statistics. We applied no other methods of within-study variability assessment. We reported risk of bias, but did not apply methods to account for potential bias beyond the specified subgroup analyses comparing results by study design. We assessed publication bias by assessing funnel plots for asymmetry.

Because of common interest in the effect of duty hour requirements on resident wellbeing and of mindfulness-based and stress management-focused approaches, we considered meta-analyses of these specific interventions for each outcome. We based the primary analyses on the first study measurement after conclusion of the intervention. However, because when the effect of each intervention might be maximised is unknown, for trials reporting results at multiple timepoints, we did sensitivity analyses including results from other timepoints for each study in separate models. We used Review Manager 5.3 software for all analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and CPW, LND, and TDS had final responsibility for the decision to submit for publication.

Results

Our search strategy identified 2617 articles, of which 230 met the criteria for full-text review (figure 1). The characteristics of the included studies are summarised in the appendix. 15 randomised controlled trials including 716 physicians^{27–41} and 37 unique cohort studies including 2914 physicians^{42–79} met eligibility criteria. Agreement between reviewers for study inclusion was high ($\kappa=0.83$). Among the 15 randomised controlled trials, three involved structural interventions within the work environment, consisting of shortened attending rotation length,³³ various modifications to clinical work processes,³⁸ and shortened resident shifts.³⁹ 12 involved individual-focused interventions, consisting of facilitated small group curricula,^{27,36,37,40,41} stress management and self-care training,^{28,30,32,34} communication skills training,^{29,31} and a so-called belonging intervention.³⁵ Four of these studies indicated funding or coverage for physicians to participate during the workday.^{28,36,40,41} Seven studies involved resident physicians (consisting of fields of internal medicine,^{31,40} paediatrics,^{30,32} and general surgery³⁵ [fields not reported in two studies^{37,39}]) and seven involved practising physicians (consisting of fields of internal medicine or primary care^{33,36,38,41} and oncology²⁹ [fields not reported in two studies^{37,39}]).

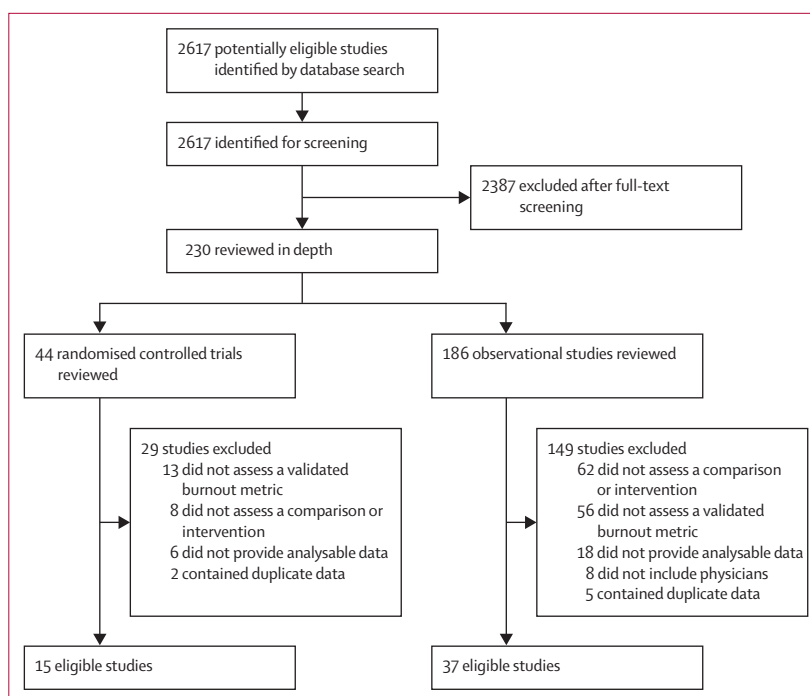


Figure 1: Study selection

Among the 37 cohort studies, 17 involved structural interventions, consisting of USA duty hour requirements^{45–47,50–52,54,61,63,78} and practice delivery changes.^{49,53,65,66,68,71,79}

20 involved individual-focused interventions, consisting of facilitated and non-facilitated small group curricula,^{43,48,55,56,58–60,62,64,69,70,73,74} stress management and self-care training,^{42,72} communication skills training,^{43,58,69,73} and mindfulness-based approaches.^{44,57,67,75–77} Only four of the cohort studies indicated funding or coverage for physicians to participate during the workday.^{49,60,64,76} 19 studies involved resident physicians (consisting of fields of internal medicine,^{46,47,65,78} surgical disciplines,^{45,50,51,75} paediatrics,^{54,61} obstetrics and gynaecology,^{56,60} family medicine,⁴⁴ neurology,⁶³ oncology,⁶⁴ and multiple specialties^{52,72,76} [field not reported in one study⁶⁷]) and 20 involved practising physicians (consisting of fields of internal medicine or primary care,^{42,48,53,57,66,74,79} oncology,^{43,58,73} intensive care,^{49,71} surgical disciplines,^{45,50} palliative medicine,⁷⁷ and multiple specialties^{55,59,62,67,70}).

All of the randomised controlled trials assessed results immediately after the conclusion of the intervention. Additional follow-up analyses were done in five studies,^{27–29,36,41} ranging from 19 weeks²⁷ to nearly 4 years²⁸ later. The Maslach Burnout Inventory¹ was applied as the burnout measure in all randomised studies but one (which used a single-item measure assessing emotional exhaustion).³⁸ Among the cohort studies, additional follow-up analyses were done in four studies,^{57,59,76,77} occurring between 1 month⁶ and 2 years⁵⁹ after the conclusion of the intervention. All but three of the cohort studies^{75,76,79} applied the Maslach Burnout Inventory.

For the five randomised controlled trials and nine cohort studies reporting differences in overall burnout, the pooled mean difference estimate was a significant absolute reduction from 54% to 44% (difference 10% [95% CI 5–14]; $p < 0.0001$; $I^2 = 15\%$; figure 2). Results did not differ for randomised controlled trials versus observational studies ($p = 0.60$; $I^2 = 0\%$) or for residents versus practising physicians ($p = 0.86$; $I^2 = 0\%$), but structural or organisational interventions were more effective than were individual-focused ones ($p = 0.03$; $I^2 = 79\%$; appendix). The six studies of duty hour requirements^{46,47,52,54,61,78} yielded a similar estimated pooled burnout reduction among residents from 62% to 50% (12% [6–17]; $p < 0.0001$; $I^2 = 28\%$). Only two studies of mindfulness-based or stress management-focused interventions addressed overall burnout,^{32,72} with a similar but non-significant estimated reduction from 34% to 28% (6% [–2 to 14]; $p = 0.14$; $I^2 = 0\%$).

For the 12 randomised controlled trials and 28 cohort studies reporting differences in emotional exhaustion score as a continuous variable, the pooled mean difference estimate was a significant 2.65 point reduction (95% CI 1.67–3.64; $p < 0.0001$; $I^2 = 82\%$) in emotional exhaustion domain score from 23.82 points to 21.17 points (figure 3). Results did not differ for randomised controlled trials versus observational studies ($p = 0.55$; $I^2 = 0\%$), residents versus practising physicians ($p > 0.99$; $I^2 = 0\%$), or structural or organisational versus individual-focused interventions ($p = 0.69$; $I^2 = 0\%$; appendix). Within the cohort studies, heterogeneity was smallest across the four studies assessing the effect of the 2003 duty hour requirements,^{45,47,50,51} with a mean reduction in emotional exhaustion score from

22.98 points to 20.10 points (difference 2.88 points [95% CI 1.17–4.59]; $p = 0.0001$; $I^2 = 5\%$). The five studies of duty hour requirements overall^{45,47,50,51,63} yielded a similar but non-significant pooled emotional exhaustion score reduction estimate from 23.01 points to 20.49 points (2.52 points [–0.28 to 5.31]; $p = 0.08$; $I^2 = 49\%$). The 11 studies of mindfulness-based or stress management-focused interventions^{28,30,32,34,42,44,57,67,75–77} yielded a somewhat greater estimated pooled score reduction than did those of other interventions from 24.64 points to 19.96 points (4.68 points [2.84–6.51]; $p < 0.0001$; $I^2 = 47\%$).

For the 11 randomised controlled trials and 25 cohort studies reporting differences in depersonalisation score as a continuous variable, the estimated pooled mean difference was a significant 0.64 point reduction (95% CI 0.15–1.14; $p = 0.01$; $I^2 = 58\%$) in depersonalisation domain score from 9.05 points to 8.41 points (figure 4). Results did not differ for randomised controlled trials versus observational studies ($p = 0.51$; $I^2 = 0\%$), residents versus practising physicians ($p = 0.91$; $I^2 = 0\%$), or structural or organisational versus individual-focused interventions ($p = 0.33$; $I^2 = 0\%$; appendix). Within the cohort studies, heterogeneity was lowest across the four studies assessing the effect of the 2003 duty hour requirements,^{45,47,50,51} with a mean reduction in depersonalisation score from 12.89 points to 11.36 points (difference 1.53 points [95% CI 0.24–2.81]; $p = 0.02$; $I^2 = 0\%$). The ten studies of mindfulness-based or stress management-focused interventions^{28,30,32,34,42,57,67,75–77} yielded a somewhat greater estimated pooled score reduction than did those of other interventions from 8.54 points to 6.53 points (2.01 points [1.34–2.67]; $p < 0.0001$; $I^2 = 0\%$).

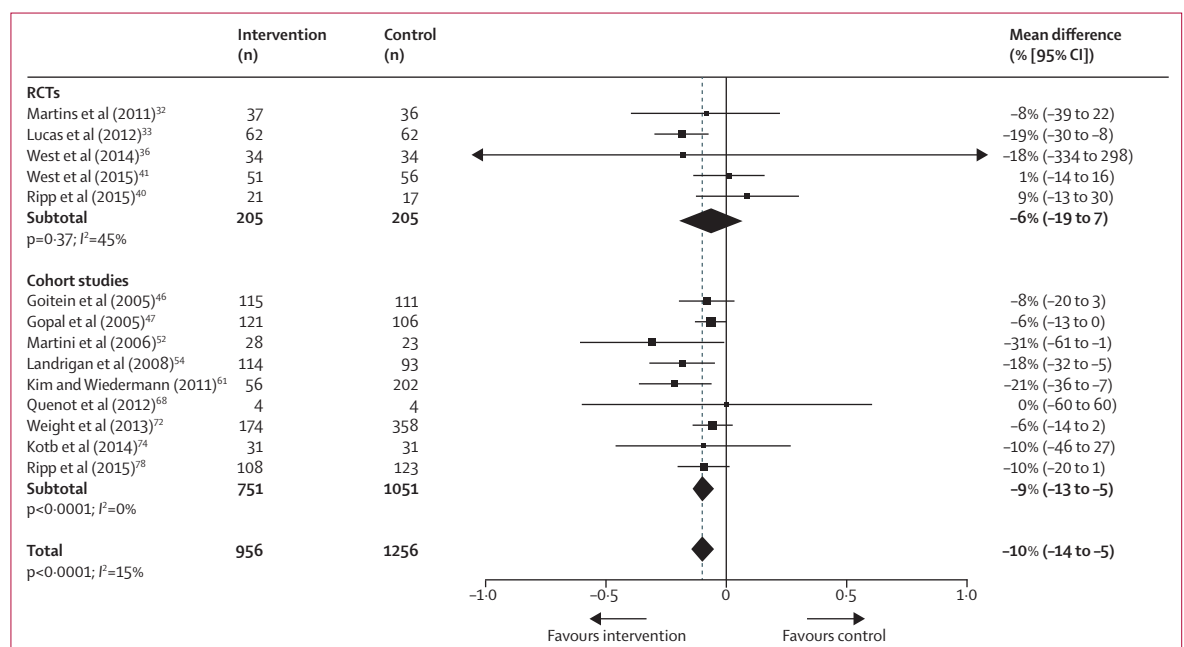


Figure 2: Overall burnout
RCT= randomised controlled trial.

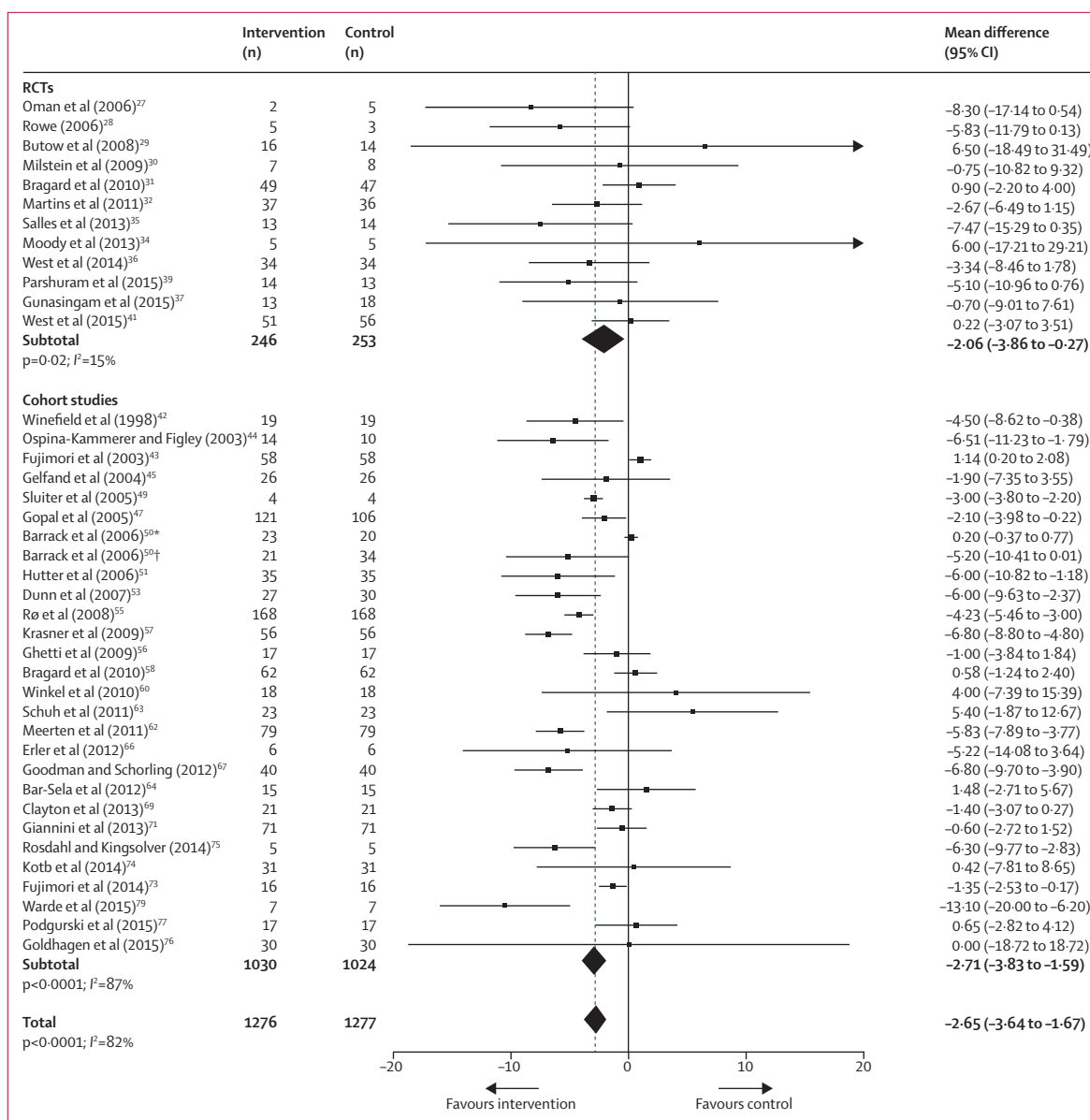


Figure 3: Emotional exhaustion score
 RCT=randomised controlled trial. *Staff. †Residents.

For the eight randomised controlled trials and 13 cohort studies reporting differences in high emotional exhaustion, the pooled mean difference was a significant absolute reduction from 38% to 24% (difference 14% [95% CI 11–18]; *p*<0.0001; *I*²=0%; appendix). Results did not differ for randomised controlled trials versus observational studies (*p*=0.79; *I*²=0%) or for structural or organisational versus individual-focused interventions (*p*=0.97; *I*²=0%), but interventions among practising physicians were more effective than were those among residents (*p*=0.006; *I*²=87%; appendix). The four studies of duty hour requirements overall^{45–47,78} yielded a similar pooled estimated high emotional exhaustion reduction from 37% to

25% (12% [5–19]; *p*<0.0001; *I*²=0%). The four studies of mindfulness-based or stress management-focused interventions^{30,34,44,72} yielded a similar but non-significant estimated pooled high emotional exhaustion reduction from 27% to 17% (10% [–1 to 21]; *p*=0.07; *I*²=27%).

For the six randomised controlled trials and ten cohort studies reporting differences in high depersonalisation, the pooled mean difference was a significant absolute reduction from 38% to 34% (difference 4% [95% CI 0–8]; *p*=0.04; *I*²=0%; appendix). Results did not differ for randomised controlled trials versus observational studies (*p*=0.33; *I*²=0%), residents versus practising physicians (*p*=0.34; *I*²=0%), or structural or organisational versus

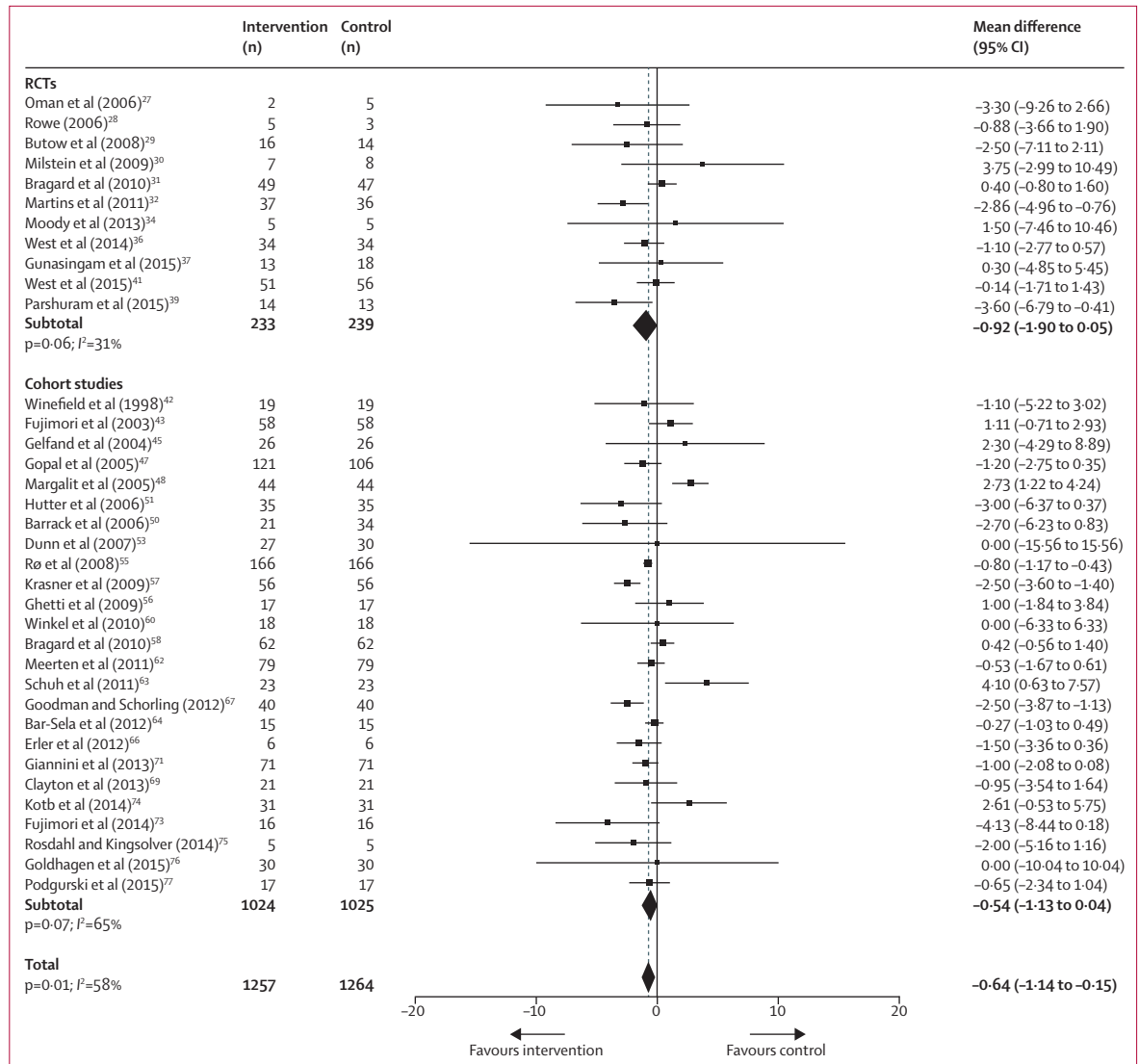


Figure 4: Depersonalisation score
RCT=randomised controlled trial.

individual-focused interventions (p=0.61; I²=0%; appendix). The four studies of duty hour requirements overall^{45-47,78} yielded a similar estimated pooled high depersonalisation reduction from 54% to 48% (6% [0-13]; p=0.04; I²=0%). The three studies assessing the effect of mindfulness-based or stress management-focused interventions on high depersonalisation^{30,34,72} yielded a similar but non-significant pooled reduction estimate from 21% to 16% (5% [-2 to 12]; p=0.13; I²=0%).

Of the 52 included studies, 47 (90%) reported no adverse events associated with the examined interventions. One study³³ reported negative effects of short attending rotations on resident assessments of faculty and four studies^{46,47,51,63} reported negative effects of duty hour requirements on subjectively assessed resident skills, resident education, and patient care (table). The assessed

risk of bias for each included study is shown in the appendix. The randomised studies inconsistently reported details of randomisation processes and uniformly lacked masking of participants to the interventions, as would be expected because of the nature of the interventions. Other potential biases were generally addressed well, and overall risk of bias appeared similar between studies. The observational studies were generally markedly limited by potential for confounding as most of these studies involved a pre-post assessment without a separate control group. Publication bias was not evident for any outcome as assessed through examination of symmetry in funnel plots (data not shown). For the separate meta-analyses of duty hour requirements and mindfulness-based and stress management-focused approaches and for sensitivity analyses including results from other timepoints for each

	Intervention	Physician sample demographics	Adverse event description
Lucas et al (2012) ³³	Short (2 week) inpatient attending rotation (4 week rotation control)	n=62 (crossover trial); 52% men; median age 38 years (range 29–55); general medicine inpatient attending physicians; USA	Decreased perceived ability by residents and medical students of attendings to fairly assess trainees and decreased summary assessments of attendings by medical students
Goitein et al (2005) ⁴⁶	2003 USA DHR	pre-DHR n=115; post-DHR n=111; 47% men; mean age NR; internal medicine residents; USA	Increased negative reported effects on patient care and resident education
Gopal et al (2005) ⁴⁷	2003 USA DHR	pre-DHR n=121; post-DHR n=106; pre-DHR 48% men; mean age NR; post-DHR 42% men; internal medicine residents; USA	Decreased overall resident satisfaction with the training programme
Hutter et al (2006) ⁵¹	2003 USA DHR	n=35; sample demographics NR; surgical residents; USA	Decreased assessment by faculty of residents' technical skills, clinical judgment, efficiency, and professionalism
Schuh et al (2011) ⁵³	2008 USA DHR (2003 USA DHR control); 1 month under each DHR set	n=23; mean age 30 years (SD 3); 44% men; neurology residents; USA	Decreased resident assessment of ability to provide continuity of care and of knowledge of patients and decreased faculty assessments of residents' clinical skills and patient care

DHR=duty hour requirements. NR=not reported.

Table: Adverse events

study in separate models, none of the results differed substantially from the primary analysis results (data not shown).

Discussion

Most studies in this systematic review and meta-analysis reported on changes in burnout domain scores, finding a significant reduction in emotional exhaustion and depersonalisation scores. Fewer studies reported on changes in overall burnout or high burnout levels in each domain than on changes in burnout domain scores, finding a significant reduction in absolute burnout and in a high degree of emotional exhaustion and depersonalisation. These effects were consistent between randomised controlled trials and observational studies, allowing pooling of results across the full range of eligible studies. Results were also similar for individual-focused and structural or organisational interventions for all outcomes other than overall burnout and for practising physicians and residents for all outcomes other than high emotional exhaustion. Heterogeneity across all studies for each of these outcomes was low, but the I^2 values for these subgroup analyses were high, suggesting that these results might reflect genuine subgroup differences worthy of further exploration.

If applied to 2014 national data for US physicians,⁶ an absolute reduction in burnout of 10% (from 54% to 44%) would represent an 18% relative risk reduction in burnout. An absolute reduction in high degree of emotional exhaustion of 14% (from 47% to 33%) would represent a 30% relative risk reduction and an absolute reduction in high degree of depersonalisation of 4% (from 35% to 31%) would represent a 12% relative risk reduction. These effects would return burnout in each domain to levels near or even below those previously reported from 2011 national data.⁵ Although the magnitude of the reductions in burnout domain scores appears modest, evidence has linked 1 point changes in burnout scores with meaningful differences in important adverse outcomes.^{8,9,12,15} Additionally, the cutoffs between

average and high burnout scores span narrow ranges. For example, a high depersonalisation burnout score is 10 or greater, with a fairly narrow range of average depersonalisation burnout scores of 6–9.¹ Therefore, reductions of only 1 or 2 points could offer benefits across the full continuum of burnout scores and could signal meaningful shifts in burnout severity category. This point is illustrated by the three most precise studies^{36,41,47} reporting differences in both mean depersonalisation score and high depersonalisation. Investigators of these studies found reductions in mean depersonalisation score of 1.2 points or fewer, which translated to 6–17% reductions in absolute proportions of a high degree of depersonalisation.

Our results substantiate that both individual-focused and structural or organisational interventions can reduce physician burnout. Although no specific physician burnout interventions have been shown to be better than are other interventions, both strategies are probably necessary. However, their combination has not been studied. The most commonly studied interventions have involved mindfulness, stress management, and small group discussions, and the results suggest that these strategies can be effective approaches to reduce burnout domain scores. Duty hour limitation policies also appear effective, although, at present, these results are derived only from observational studies in the USA.

Various carefully planned approaches seem useful, which is reassuring for individuals and organisations contemplating tackling physician burnout. However, this study makes clear that much additional research into interventions for physician burnout is necessary. For example, although heterogeneity in results across intervention types was generally modest, data are insufficient to fully delineate which classes of interventions might be most effective. Randomised studies of structural or organisational interventions have been uncommon, with only three^{33,38,39} reported in the literature to date. Additional studies are particularly

needed in this domain. Which interventions offer the greatest value to physicians and their organisations remains unclear, as well as whether or not the processes involved in development and deployment of interventions could influence their effectiveness. For example, relative to externally developed approaches, interventions for which physicians in the local work environment are engaged in design and implementation might heighten their sense of control and engagement, which might be expected to effectively reduce burnout.⁸⁰ Our data are not adequate to address this hypothesis, however. Future research into organisational interventions to reduce physician burnout should address the optimal approaches to development and implementation of burnout reduction strategies, along with assessment of the feasibility and costs associated with these interventions.

Additionally, few studies have assessed long-term or post-intervention effects. The results of these assessments generally suggest sustained or even augmented benefits for many months after completion of the studied intervention,^{28,36,41,55,57,59,77} but this finding is not universal.²⁷ Whether or not potentially beneficial interventions require periodic re-exposure to sustain or maximise their effects or how frequently such re-exposure should occur is unknown.

This study has limitations. Data for participant demographics were only sporadically reported in the included studies, and the possibility of differing intervention effects for different participant subgroups remains largely unaddressed. Also, many of the included cohort studies had substantial risk of bias, largely due to low ability to control for potential confounding factors. However, the overall quality of the randomised trials in this review was moderate, and despite their methodological differences and limitations, the observational studies and randomised trials yielded statistically similar results.

Additional research is needed to clarify categories of beneficial interventions to reduce physician burnout, which interventions or combinations of interventions might be most effective, and optimal approaches to development and implementation of these interventions. Rigorous, well-designed, generalisable studies addressing these questions are now needed to build on this early foundation of evidence to expand understanding of interventions to address the pervasive problem of physician burnout.

Contributors

CPW, LND, and TDS designed the study and acquired, analysed, and interpreted data. PJE did the literature search and interpreted data. CPW drafted the manuscript, with critical revisions for important intellectual content from all authors.

Declaration of interests

We declare no competing interests.

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