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Effects and moderators of exercise on sleep in adults with cancer: Individual patient data and aggregated meta-analyses

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Abstract

Objectives
To evaluate the effects of exercise interventions on sleep disturbances and sleep quality in patients with mixed cancer diagnoses, and identify demographic, clinical, and intervention-related moderators of these effects.

Methods
Individual patient data (IPD) and aggregated meta-analyses of randomized controlled trials (RCTs). Using data from the Predicting OptimaL cAncer RehabIlitation and Supportive care project, IPD of 2173 adults (mean age = 54.8) with cancer from 17 RCTs were analyzed. A complementary systematic search was conducted (until November 2018) to study the overall effects and test the representativeness of analyzed IPD. Effect sizes of exercise effects on self-reported sleep outcomes were calculated for all included RCTs. Linear mixed-effect models were used to evaluate the effects of exercise on post-intervention outcome values, adjusting for baseline values. Moderator effects were studied by testing interactions for demographic, clinical and intervention-related characteristics.

Results
For all 27 eligible RCTs from the updated search, exercise interventions significantly decreased sleep disturbances in adults with cancer (g = -0.09, 95% CI [-0.16; -0.02]). No significant effect was obtained for sleep quality. RCTs included in IPD analyses constituted a representative sample of the published literature. The intervention effects on sleep disturbances were not significantly moderated by any demographic, clinical, or intervention-related factor, nor by sleep disturbances.

Conclusions
This meta-analysis provides some evidence that, compared to control conditions, exercise interventions may improve sleep disturbances, but not sleep quality, in cancer patients, although this effect is of a small magnitude. Among the investigated variables, none was found to significantly moderate the effect of exercise interventions on sleep disturbances.

Keywords
cancer; physical activity; treatment, sleep

Introduction

Sleep disturbances, and more specifically insomnia, are amongst the most prevalent symptoms associated with cancer [1]. Sleep disturbances have been defined as disruptions in nighttime sleep or wakefulness that include a variety of clinical disorders (e.g., insomnia, hypersomnolence, restless leg syndrome disorder) and are intensified during cancer treatments [2]. Between 30 and 60% of cancer patients report insomnia symptoms at some point during their cancer care trajectory [3,4]. Insomnia is also a highly persistent problem in this population, with a persistence rate of 64% on 2- to 4-month intervals [4]. A poor sleep quality (defined as a "subjective perceptions about one's sleep" [5]) has been found in 48% to 60% among adults with breast or neck cancer [6,7]. It is therefore essential to provide effective treatments to reduce sleep disturbances such as insomnia and to improve sleep quality in cancer patients.

The various beneficial effects of exercise have extensively been investigated in adults with cancer. Exercise interventions significantly improve health-related quality of life [8–11], physical fitness [9–12], lean body mass [13], fatigue [14,15], depressive symptoms [16], and anxiety [17] during and after cancer treatment. It has also been demonstrated that exercise is safe and well tolerated in this population even during cancer treatments [18].

Exercise may also have a positive impact on sleep. Two previous meta-analyses including randomized controlled trials (RCTs) found that exercise interventions significantly reduced sleep disturbances in adults with cancer but with effects sizes of a small magnitude [10,19]. However, the risk of selection bias was high in these meta-analyses given that they selected studies that had looked at the effect of exercise on quality of life and fatigue. More recently, a third meta-analysis found no significant benefit of exercise interventions on self-reported sleep quality (measured with the Pittsburgh Sleep Quality Index [PSQI] or General Sleep Disturbance Scale) and two objectively-assessed sleep parameters (i.e., sleep-onset latency and sleep efficiency) in patients with cancer [20].

Inconsistent conclusions from previous meta-analyses on the effect of exercise on sleep could be explained by participants or exercise interventions heterogeneity between or within included RCTs. Ancillary analyses carried out in a few studies showed that some clinical (e.g., baseline severity of sleep disturbances), personal (e.g., body mass index [BMI]), and cancer-related (e.g., chemotherapy, cancer type) factors moderated the effects of exercise interventions on health-related quality of life [21,22]. Exercise intervention characteristics (e.g., dose, type, duration) have also been found to influence intervention effects on sleep [23,24]. However, these moderating analyses were generally not planned *a priori* and were often conducted with insufficient statistical power.

Meta-analyses of individual patient data (IPD) are particularly recommended to study moderators of intervention effects [25]. IPD meta-analyses typically investigate the possible role of participants' demographic and clinical characteristics (e.g., age, stage of disease) and characteristics of the intervention [26]. An IPD meta-analysis also permits to disentangle subject-level and study-level sources of heterogeneity in treatment effects [27]. To our knowledge, no IPD has been performed to examine the moderators of exercise effects on sleep. The Predicting OptimaL cAancer RehabIlitation and Supportive care (POLARIS) dataset [28] provides a unique opportunity to assess the effects of exercise interventions on sleep and their moderators in the context of cancer.

The aims of this study were to evaluate the effects of exercise interventions on sleep disturbances and sleep quality in patients with cancer, and to investigate whether the exercise intervention effects are moderated by demographic, clinical, and intervention-related factors, and baseline sleep disturbances.

Method

The conduct and reporting of this IPD meta-analysis were based on the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) statement [29].

Identification and inclusion of studies

The POLARIS project includes RCTs that evaluated the effects of exercise interventions and/or psychosocial interventions on quality of life as compared to a wait-list, usual care or attention control group in adult patients with cancer. For the purpose of this study, only RCTs on exercise interventions with sleep outcomes were included. Potential studies for inclusion in the POLARIS database were identified in September 2012 via systematic searches in four electronic databases (PubMed, EMBASE, PsycINFO, and CINAHL), reference checking of systematic reviews, and meta-analyses. After principal investigator's of selected studies expressed interest in data sharing, they were requested to sign a data sharing agreement stating that they agreed with the POLARIS policy document, and were willing to share anonymized data of

study participants who were randomized. Data could be sent in various formats, were re-coded according to standardized protocols, and were checked for completeness, improbable values, consistency with published articles, and missing items. Subsequently, datasets were imported into the POLARIS database where they were harmonized [28]. A detailed description of the design and procedures of the POLARIS study was previously published [8,28].

To determine whether the exercise effect on sleep outcomes based on individual data was substantially affected by selective reporting bias, the representativeness of studies was tested [30]. More specifically, we compared the pooled effect sizes obtained in RCTs that had provided IPD to the POLARIS database and those with no available individual data. As already stated, the POLARIS study was initially designed to include RCTs with quality of life outcomes [28]. Consequently, a complementary search strategy was completed to identify RCTs not included in the POLARIS database but reporting the effects of exercise interventions on sleep in the cancer context. Reference lists of relevant systematic reviews [10,19,20] were also searched. Finally, Pubmed and PsycArticles were consulted to identify the most recent RCTs published between May 2016 and November 2018. Details about the search strategy are presented in the Supplementary File.

To be included in the current meta-analysis, RCTs had to contain a validated measure of sleep disturbances or sleep quality. Sleep disturbances depict the individual perception of negative consequences from sleep fragmentation during night time and short sleep duration [31]. Sleep quality represents the subjective nature of individuals' sleep habits (i.e., asleep easily, sufficient sleep duration, wake-up feeling rested, no sleepiness during wake time) [31].

Data extraction

The study characteristics and quality of included studies were rated by two independent reviewers (LB, MS) and any discrepancies were resolved by discussion [8] The methodological quality of each trial was examined using six criteria: random sequence generation, allocation concealment, incomplete outcome, incomplete reporting, exercise adherence and contamination. More details have previously been published [8].

Sleep disturbances were measured with the single item "*During the past week, have you had trouble sleeping ?*" from the European Organization for Research and Treatment of Cancer Quality of Life – Core 30 questionnaire (EORTC QLQ-C30) [32]. This item is rated on a 1 to 4 scale: "not at all" (coded as 1), a little, quite a bit, and very much" (coded as 4). It has previously been used to determine the prevalence and trajectories of sleep disturbances in cancer patients [33–36], but also as an outcome measure in RCTs examining the effects of cancer treatment [37] and psychotherapy [38]. Sleep quality was assessed with the PSQI. This questionnaire is a commonly used 19-item psychometrically validated measure of sleep quality [39].

Representativeness of included studies

To examine whether the included RCTs were a representative sample of all eligible RCTs, we compared pooled effect sizes of RCTs included in the POLARIS database versus those not included or identified in our complementary search strategy. The standardized mean difference effect size was calculated for self-reported sleep outcomes using the pooled standard deviation of the treatment and control conditions at post-treatment of RCTs only [27]. Between-group effect sizes were weighted according to the sample size, thus yielding Hedges' *g*. Regression residuals were screened to identify potential multivariate outliers using residual Cook distances. A possible publication bias was evaluated by examining funnel plot and testing asymmetry with Egger's test ($p < 0.10$ indicating a publication bias) (Higgins et al., 2003). A contour enhanced funnel plot with areas of statistical significance ($p = .10$, $p = .05$, $p = .01$), was constructed to visualize the pattern of statistical significance in included RCTs [40]. A trim and fill analysis was also carried out to examine the impact of missing studies by adjusting the meta-analysis to take into account the theoretically missing studies [41]. Both estimates representing RCTs with aggregated data and with IPD were compared in a fixed-effects model with a dummy variable for each estimate [42].

Potential moderators

Based on the authors' clinical and research expertise, literature search, and distribution of characteristics in included studies, the following characteristics were tested as possible moderators of intervention effects on the sleep impairment measure [8,22–24,43,44] : (1) demographic characteristics including age, sex, marital status and education level; (2) clinical variables including body mass index, cancer type (i.e., breast, male genitourinary, gastrointestinal, hematological, gynecological, respiratory tract, other types), presence of distant metastases and type of cancer treatment; and (3) exercise intervention

characteristics including timing of intervention delivery in relation to primary cancer treatment (i.e., during treatment, post-treatment), delivery mode of intervention (i.e., supervised or unsupervised exercise sessions), intervention duration (≤12 weeks; between 12–24 weeks; >24 weeks), exercise intensity (from light to high), exercise type (i.e., aerobic, resistance or combined), and duration of exercise sessions (categorized into ≤30 min, between 30–60 min, >60 min). Regarding sleep quality data, only one moderator was tested: the presence of sleep difficulty. Because a clinical cut-off score only exists for the PSQI (>5), the moderating role of the presence of a clinical level of sleep difficulties (or poor sleeper status) at baseline was only investigated in RCTs assessing sleep quality with that questionnaire. As recommended, participants were categorized as poor sleepers when their PSQI score was greater than 5 [39]. Other demographic and clinical factors were not testable in analyses on RCTs that measured sleep quality because of highly heterogeneous methodological features across studies: one trial included cancer with mixed cancer types [45] and the other two trials included participants during chemotherapy [46] or combined treatments [47].

Statistical analyses

A one-step IPD meta-analysis was carried out to study the effects and moderators of effects of exercise interventions on self-reported sleep disturbances and sleep quality. The effects were evaluated by regressing the intervention on the post-intervention value (z-score) of the outcome adjusted for the baseline value (z-score) using linear mixed model analyses with a two-level structure (1: patient; 2: study) to take into account the clustering of patients within studies by using a random intercept on study level [27]. For each potential moderator, the carried out mixed model analysis included the variable and its interaction with the intervention. When the likelihood ratio test of the model with and without the interaction term was significant ($p < 0.05$), stratified analyses were conducted in the strata that included data from more than one RCT [48]. Regression coefficients and 95% confidence intervals (CI) were reported, representing the between-groups difference in z-scores of sleep disturbances and sleep quality. These correspond to Cohen's *d* effect sizes effects of 0.2 are considered small, 0.5 as moderate and of 0.8 or greater as large. Statistical analyses were performed using *metafor [49]* and *nlme* [50] packages, for meta-analyses on aggregate data and linear mixed model analyses, respectively, in R v3.3.

Results

Search strategy

Principal investigators of 34 of 69 eligible RCTs for the POLARIS project (response rate: 49%) shared IPD, of which 17 RCTs (n = 2173) had sleep outcomes. Among them, 16 RCTs (n = 2047) had sleep disturbances data and, 3 RCTs (n = 610) had sleep quality data. Two RCTs had sleep disturbances and sleep quality data (n = 484) [45,46] and one RCT had only sleep quality (n = 126) [47] (see details in the supplementary file). Two RCTs reported sleep duration data [44,51] and one RCT had sleep wake data [44] (not included in analyses).

The complementary search of more recent studies retrieved, 11 RCTs assessing sleep disturbances and 14 RCTs reporting sleep quality data . More details are available in the supplementary file. Overall, published summary data for sleep disturbances and sleep quality were available for 16/27 RCTs (16 RCTs from the POLARIS database + 11 RCTs from the complementary search) and 3/17 RCTs (3 RCTs from the POLARIS database + 14 RCTs from the complementary search), respectively.

Characteristics of studies with individual data

The mean age of participants in the 17 RCTs was 54.8 (SD =11.3), 63% were women and 52% were diagnosed with breast cancer and 76.5% received supervised exercise sessions (see details in Table 1). The sample size of each study ranged from 51 to 277. The duration of interventions ranged from 12 to 52 weeks. In total, 14 RCTs reported an adequate random sequence generation, 13 RCTs reported an adequate allocation concealment method, 14 RCTs had adequate completeness of outcome data, and 4 RCTs had a complete outcome reporting (see details in the supplementary file – Table S1). Evaluation of intervention adherence was reported in 13 RCTs, and was of a high quality in 6 RCTs, and 2 of the 5 RCTs that provided information on contamination met the criterion for high quality. Table 2 presents mean values obtained on sleep outcomes in both intervention and control arms in RCTs from the POLARIS database.

Table 1
Demographic, clinical and intervention-related characteristics of participants in the exercise and control group (POLARIS)

	Intervention (n = 1220)	**Control (n = 953)***
Demographic		
Age M (SD)	54.7 (12.1)	54.9 (11.9)
Age categories n (%)		
< 50 years	390 (32)	320 (33.6)
50-70 years	659 (54)	505 (53)
≥ 70 years	170 (13.9)	125 (13.1)
Unknown	1 (0.1)	3 (0.3)
Sex n (%)		
Male	454 (37.2)	355 (37.3)
Female	766 (62.8)	598 (62.7)
Married/living with partner n (%)		
No	203 (16.6)	175 (18.4)
Yes	903 (74.0)	663 (69.6)
Unknown	114 (9.3)	115 (12.1)
Education level n (%)		
High	488 (40.0)	335 (35.2)
Low/middle	611 (50.1)	501 (52.6)
Unknown	121 (9.9)	117 (12.3)
Clinical		
BMI M (SD)	26.6 (4.5)	26.9 (4.7)
BMI categories n (%)		
Underweight (BMI <18.5 kg/m^2)	5 (0.4)	8 (0.8)
Normal weight (BMI 18.5 to <25 kg/m^2)	385 (31.6)	270 (28.3)
Overweight (BMI 25 to <30 kg/m^2)	391 (32.0)	289 (30.3)
Obese (BMI > 30 kg/m^2)	198 (16.2)	163 (17.1)
Unknown	241 (19.8)	223 (23.4)
Cancer type n (%)		
Breast	490 (51.4)	631 (51.7)
Male genitourinary	317 (26)	238 (25.0)
Haematological	128 (13.4)	138 (11.3)
Gastrointestinal	77 (6.3)	54 (5.7)
Gynecological	41 (3.4)	32 (3.4)
Respiratory tract	2 (0.2)	4 (0.4)
Other	14 (1.1)	7 (0.7)
Distant metastases at baseline n (%)		
No	1042 (85.4)	802 (84.2)
Yes	41 (3.4)	32 (3.4)
Unknown	139 (11.4)	129 (13.5)
Surgery n (%)		
No	210 (17.2)	159 (16.7)
Before the intervention	765 (62.7)	564 (59.2)
During the intervention	65 (5.3)	64 (6.7)
Unknown	180 (14.8)	166 (17.4)
Chemotherapy n (%)		
No	364 (29.8)	289 (30.3)
Before the intervention	373 (30.6)	279 (29.3)
During the intervention	420 (34.4)	326 (34.2)
Unknown	63 (5.2)	59 (6.2)

Radiotherapy n (%)		
No	509 (41.7)	371 (38.9)
Before the intervention	395 (32.4)	281 (29.5)
During the intervention	253 (20.8)	254 (26.5)
Unknown	62 (5.1)	48 (5.0)
Hormone therapy for breast cancer n (%)		
No	210 (17.2)	175 (18.4)
During the intervention	235 (19.3)	132 (13.9)
Unknown	775 (63.5)	646 (67.8)
Hormone therapy for prostate cancer n (%)		
No	11 (1.2)	16 (1.3)
Before the intervention	48 (3.9)	47 (4.9)
During the intervention	198 (16.2)	128 (13.4)
Unknown	958 (78.5)	767 (80.5)
Exercise intervention		
Timing of intervention n (%)		
During treatment	729 (59.8)	-
Post treatment	451 (37.0)	-
Pre-during-post treatment	40 (3.0)	-
Mode of intervention delivery n (%)		
Unsupervised	287 (23.5)	-
Supervised	933 (76.5)	-
Duration of intervention n (%)		
<=12 weeks	486 (39.8)	-
>12-24 weeks	432 (35.4)	-
> 24 weeks	262 (21.5)	-
Unknown	40 (3.3)	-
Exercise intensity n (%)		
Low-Moderate	68 (5.6)	-
Moderate	334 (27.4)	-
Moderate-High	656 (53.8)	-
High	91 (7.5)	-
Unknown	71 (5.8)	-
Exercise type n (%)		
Aerobic and resistance exercise	769 (63)	-
Aerobic exercise	254 (20.8)	-
Resistance exercise	197 (16.1)	-
Exercise session duration n (%)		
≤ 30 minutes	327 (26.8)	-
>30 – 60 minutes	792 (64.9)	-
>60 minutes	101 (8.3)	-
Type of control group n (%)	-	
Usual care	-	553 (58)
Attention control	-	176 (18.5)
Wait-list control	-	224 (25.5)

Notes. M = mean; SD = standard deviation; n = number of participants; BMI = Body Mass Index

Table 2
Pre- and post--intervention values on sleep outcomes

	Intervention		Control	
	n = 1152	n = 1050	n = 895	n = 800
	Pre M (SD)	Post M (SD)	Pre M (SD)	Post M (SD)
Sleep disturbances EORTC QLQ-C30 item	29.31 (29.22)	27.65 (29.30)	30.39 (31.26)	30.42 (30.84)
	n = 396	n = 349	n = 214	n = 210
Sleep quality*				
PSQI scores	8.6 (4.0)	8.9 (3.8)	7.8 (4.2)	8.3 (4.0)
Poor sleepers (PSQI>5) n (%)	301 (76%)	286 (82%)	153 (71%)	155 (73%)

Notes. n = number of participants, M = mean, SD = standard deviation, EORTC QLQ-C30 = European Organisation Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 ; PSQI = Pittsburgh Sleep Quality Index; * = two RCTs had sleep disturbances and sleep quality data

Effects of exercise interventions on sleep outcomes (all eligible studies)

When evaluating all eligible studies (i.e., more recent RCTs with aggregated data [n = 785] and IPD [n = 2047]), participants who were randomized to an exercise intervention showed a significant larger reduction in self-reported sleep disturbances at post-treatment (*g* = -0.09, 95% CI [-0.16; -0.02]), after trim and fill adjustment) compared with patients in control groups. No significant intervention effect was observed on sleep quality when analyzing all eligible studies (i.e., more recent RCTs with aggregated data [n = 1325] and IPD [n = 610]). Data from the study by Brown et al. [52] were not included in the meta-analysis because information needed to calculate effect size. The detailed findings are shown in Table 3. The forest and funnel plots are presented in the supplementary file (Table S2).

Table 3
Representativeness of the pooled effects of studies providing sleep data for the POLARIS project and those not providing data or published between September 2012 and November 2018.

Representativeness	**k**	***g* (95 % CI)**	**Q**	I^2	***p***	**Between-groups differences**
Sleep disturbances						
All eligible studies	27	-0.09 (-0.17; -0.02)	29.2	6.6	0.01	
All eligible studies, excluding one outlier	26	-0.11 (-0.18; -0.03)	22.6	1.5	0.004	
Studies with IPD	16	-0.07 (-0.15; 0.02)	13.2	0	0.14	
Studies without IPD	11	-0.15 (-0.31; 0.02)	14.4	26.8	0.08	0.28
Studies without IPD, excluding one outlier	10	-0.22 (-0.36; -0.08)	6.08	0	0.002	0.07
Sleep quality						
All eligible studies	17	-0.09 (-0.31; 0.11)	66.09	79.1	0.37	
All eligible studies, excluding two outliers	15	-0.04 (-0.11; 0.19)	25.7	54	0.61	
Studies with IPD	3	0.12 (-0.13; 0.37)	4.6	57	0.35	
Studies without IPD	14	-0.17 (-0.43; 0.09)	58.1	79	0.27	0.26
Studies without IPD, excluding two outliers	12	-0.003 (-0.19; 0.19)	24.9	54	0.97	0.49
Publication bias	$K_{missing}$	**Adjusted effect**	**P Egger**		***p***	
Sleep disturbances						
All eligible studies	3	-0.09 (-0.16; -0.02)	0.30		0.02	
Studies with IPD	4	-0.02 (-0.10; 0.07)	0.18		0.70	
Studies without IPD	0	-0.22 (-0.36; -0.08)	0.62		0.002	
Sleep quality						
All eligible studies	0	-0.04 (-0.11; 0.19)	0.45		0.61	
Studies with IPD	0	0.12 (-0.13; 0.37)	0.05		0.35	
Studies without IPD	0	-0.003 (-0.19; 0.19)	0.48		0.93	

Notes.
CI = confidence interval; *g* = Hedges' g effect size; I^2 = I^2 statistic, which is the percentage of total variance that can be explained by heterogeneity, and 25% is considered low, 50% moderate, and 75% high heterogeneity; k = number of exercise intervention arms; Q = Q-test for heterogeneity, which is significant if there is evidence for heterogeneity

Representativeness and publication bias

No significant differences were found in exercise effects on sleep quality between RCTs with IPD available and those with no IPD available (Table 3). However, when using sleep disturbances as the dependent variable, the effect size was significant when aggregated data from all available RCTs were analysed (g = -0.22, 95% CI [-0.36; 0.08]) but not in the meta-analysis of IPD (g = -0.07, 95% CI [-0.15; 0.02]). The Egger test showed no significant publication bias for the sleep disturbances outcome, but a significant bias, suggesting an underestimation of the effect, was found for RCTs with IPD measuring sleep quality (Table 3).

Moderators of exercise on sleep outcomes in RCTs with individual data

None of the investigated variables were found to significantly moderate the effect of exercise interventions on sleep disturbances (see Table 4). Further, the presence of clinically significant sleep difficulties on the PSQI (score >5) did not significantly moderate the effect of exercise interventions on that measure of sleep quality.

Table 4
Possible moderators of the effects of exercise interventions on sleep disturbances

	n	Sleep disturbances (ß)	*p*
Demographic variables			
Age categories			0.10
< 50 years	847	-	
50 – 70 years	1261	-	
≥ 70 years	304	-	
Sex (women vs. men)	1835 (833 vs 1585)	-	0.13
Marital status (partner vs. single)	1751 vs 421	-	0.18
Education level (high vs. low-middle)	917 vs 1242	-	0.08
Clinical variables			
BMI categories			0.37
Underweight (BMI <18.5 kg/m2)	18	-	
Normal weight (BMI 18.5–<25 kg/m2)	777	-	
Overweight (BMI 25 to <30 kg/m2)	755	-	
Obese (BMI P30 kg/m2)	398	-	
Cancer type			0.75
Breast	1337	-	
Male genitourinary	574	-	
Haematological	272	-	
Gastrointestinal	131	-	
Gynaecological	77	-	
Other [a]	27	-	
Metastases (yes vs. no)	64 vs. 2080	-	0.52
Surgery (yes vs. no)	1683 vs. 388	-	0.19
Chemotherapy (yes vs. no)	1599 vs. 695	-	0.62
Radiotherapy (yes vs. no)	1341 vs. 934	-	0.09
Exercise intervention characteristics			
Exercise post vs. during treatment	1023 vs. 1315	-	0.12
Intervention delivery mode			
Effect supervised vs. home	943 vs. 398	-	0.11
Effect supervised vs. control	943 vs. 1077	-	0.19
Effect home vs. control	398 vs. 1077	-	0.14
Intervention duration			0.78
≤ 12 weeks	1079	-	
>12 – 24 weeks	784	-	
> 24 weeks	474	-	
Intensity			
Effect low-moderate and moderate vs. control	407 vs. 1005	-	0.52
Effect moderate-vigorous and vigorous vs. control	667 vs. 1005	-	0.36
Effect moderate-vigorous and vigorous vs. low-moderate and moderate	407 vs. 862	-	0.45
Time of session	334 vs. 906	-	0.68
>0-30min vs. >30-60min	334 vs.101	-	0.34

>0-30min vs. >60min >30-60min vs >60min	906 vs.101	-	0.38
Type			
Aerobic exercise vs. control	359 vs. 1077	-	0.23
Aerobic + resistance exercise vs. control	784 vs. 1077	-	0.35
Resistance exercise vs. control	198 vs. 1077	-	0.68

[a] Respiratory tract was combined with the “other cancer” category

Discussion

Intervention effects on sleep

The present study evaluated the effects of exercise interventions on two sleep outcomes and examined potential moderators of these effects using IPD of 2173 adults with cancer. Results of aggregated data meta-analyses of 26 RCTs (i.e., all eligible pooled RCTs) showed a significantly greater reduction of self-reported sleep disturbances after exercise interventions, as compared control groups, but with an effect size lower than a small magnitude (*g* = -0.09). Moreover, results did not show a significant effect of exercise interventions on self-reported sleep disturbances (16 RCTs) and sleep quality (3 RCTs) at post-treatment in RCTs on which IPD were provided (POLARIS project). Although, studies with no available IPD showed a significant intervention effect on self-reported sleep disturbances, no significant differences were observed between studies with and without IPD. Overall, these results suggest that studies with IPD may have underestimated the general effect of exercise interventions on self-reported sleep disturbances but that intervention effects, if they exist, are of a small magnitude. Similar differences in results from data extracted from published papers and individual data obtained from trialists have been reported in several previous meta-analyses conducted in the oncology field [53]. The lack of an exercise intervention effect on sleep quality in cancer patients (for all pooled studies or RCTs with IPD only) is consistent with the most recent meta-analysis on this question that used aggregated data [20]. However, it is important to note that this finding differs from studies conducted in adults without cancer. Indeed, Kredlow et al.[54] showed that exercise interventions were associated with a large effect (*d* = 0.74) on sleep quality.

IPD meta-analyses were carried out to identify possible moderators of exercise intervention effects on sleep outcomes. Regarding self-reported sleep disturbances, as assessed with the single sleep item of the EORTC QLQ-C30 questionnaire, neither age, sex, education level, marital status, BMI, cancer type and treatment, metastatic stage were found to significantly moderate the effects. In addition, we found no indication that intervention features such as the mode of delivery or sessions duration moderated the effect of exercise interventions on sleep disturbances. No previous IPD or aggregated meta-analyses investigated the moderators of exercise interventions on sleep [19,20,55]. It is also interesting to note that a previous POLARIS IPD meta-analysis, which studied effects of exercise interventions on quality of life, did not identify any demographic, clinical or interventional moderators of exercise interventions on that outcome either [8]. Only baseline values of quality of life had a moderator effect in the effect of exercise interventions when delivered post cancer treament [56]. These mainly null findings suggest that benefits from exercise interventions may not differ as a function of various demographic, clinical, and intervention characteristics. However, although a relatively large total sample size was available to carry out moderator analyses, the number of participants was relatively small for several patient-level moderators (e.g., cancer type which was in large part breast cancer) [57]. For sleep quality, only the presence of clinically significant sleep disturbances at baseline could be tested, due to the small number of studies that used the PSQI and the ensuing relatively small number of participants available (i.e., n = 610). Results showed no moderating effect of having a clinical level of sleep difficulties before beginning the exercise intervention, contrasting with previous findings of Courneya et al. [43] This RCT revealed that a supervised aerobic exercise training for patients with lymphoma significantly improved sleep quality, but only in participants identified as poor sleepers before the intervention [43]. These findings also differ from a recent systematic review which concluded that exercise interventions improved more importantly sleep quality in poor sleepers [58].

Areas for future research

A critical aspect that needs to be improved in future studies is the selection of sleep measures. Among studies that were reviewed in the current meta-analysis, the vast majority used the single sleep item from the EORTC QLQ C-30 questionnaire and, to the best of our knowledge, its convergent validity has not

been studied with more elaborated and validated sleep measures. In the future, measures that assess sleep disturbances more thoroughly should be used such as the Insomnia Severity Index [59] and the Sleep Disorders Questionnaire [60]. More trials should also combine self-report and objective measures of both sleep and physical activity given that initial physical inactivity or sleep disturbances can be underestimated in adults with cancer [61,62]. Additionally, interventions in RCTs with IPD data generally aimed to improve physical fitness fatigue, or other quality-of-life related endpoints, but none targeted sleep specifically as the primary outcome. An exercise intervention with the goal of improving fitness, fatigue or quality of life may be not be similarly suited to decrease sleep difficulties. Another aspect that needs to be improved in the future is the selection of patients with initial clinically significant sleep impairments to decrease the probability of a floor effect. Finally, to better understand factors that influence the effects of exercise interventions on sleep, future studies should examine participants with more diverse types of cancers, and investigate the role of individual adherence rates to exercise prescriptions [54,63].

An increasing number of peer-reviewed scientific journals adopt policies that support data sharing [61]. Thus, it is likely that more studies will be shared in the future, leading to larger IPD databases. Physical activity – sleep associations seem relatively complex and more understandable at intra-personnel level in the context of cancer [64]. Consequently, N-of-1 trials (i.e., set of single-patient within-subject trials) can identify those individual patients who respond (and those who do not) to particular exercise interventions [65]. Thus, the development of aggregated n-of-1 RCTs could provide an opportunity to identify between-participants moderators explaining the effects of exercise interventions on sleep outcomes [66].

Strengths and limitations

Strengths of this study include the relatively large number of included trials with IPD on sleep disturbances. All included RCTs in aggregated meta-analyses examined the effect of exercise interventions on sleep disturbances controlling for the influence of publication bias. This study also has several limitations that need to be acknowledged. First, although 2173 participants were included in IPD meta-analyses, the results on moderation should be interpreted with caution because sample sizes of some subgroups were small, due to coding schemes (e.g., cancer stage) or lack of information on a particular variable. Second, as already mentioned, data of only three studies were available for sleep quality analyses thus limiting the generalization of findings. Third, two important confounders could not be tested and may have introduced a bias, that is the psychotropic/sleep medication use [67] and adherence rates. The adherence rates are generally poorly reported in exercise studies with cancer survivors [68]. Fourth, it was impossible to control for a possible contamination effect in the available data. Contamination rates (i.e., patients in the control group that increase their exercise level by themselves) from 22 to 52% were reported in two RCTs testing exercise interventions in cancer patients [69,70].

Conclusion

These IPD and aggregated meta-analyses provide some evidence that exercise interventions, relative to controls, can reduce sleep disturbances in patients with cancer, but this effect may not be clinically meaningful. Moreover, the findings indicate no significant improvement of sleep quality after an exercise intervention. Among all investigated variables as possible demographic, clinical and intervention-related moderators, none was found to influence the effect of exercise interventions on sleep disturbances and sleep quality. Until future research proves differently, exercise interventions should only be considered as an adjunct therapy to other established treatments for sleep difficulties such as cognitive-behavioral therapy for insomnia. This conclusion is in line with results of a recent RCT conducted in cancer patients with clinical levels of insomnia symptoms which suggested that, while an exercise intervention had some beneficial effects on sleep, CBT-I remained the treatment of choice for cancer-related insomnia (Mercier et al., 2018).

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Supplementary file

METHOD

Identification and inclusion of studies for representativeness analyses

The search strategy was adapted for Medline and PsyArticle databases using its specific vocabulary map, employing Mesh terms that referred to "cancer", "sleep" and "exercise". The Medline search strategy first included Mesh terms related to cancer (“Neoplasm”) AND sleep ("Sleep", "Sleep Disorders", "Sleep Initiation and Maintenance Disorders") AND exercise ("Exercise", "Physical Therapy Modalities", "Motor Activity", "Exercise Therapy", "Sports"). This algorithm was then adapted to PsyArticle database.

Inclusion criteria

Participants

Studies were included if they included adult patients only (18 years and older) with a cancer diagnosis. Participants, men and women, could have any type of cancer and could be at any stage of the cancer care trajectory (during or after treatment).

Interventions

Various forms of exercise interventions were considered eligible including aerobic, resistance or a combination of both. Exercise interventions could be combined with flexibility exercises or with another type of intervention (e.g., counseling). However, yoga interventions were excluded given the large heterogeneity of yoga types, being more or less demanding physically. No restriction was made regarding frequency, intensity or duration of the program. Interventions could be unsupervised or supervised.

Comparisons

Control arms could be usual care (no exercise intervention) or an alternative intervention (e.g., relaxation).

Outcomes

RCTs had to contain at least one self-reported measure of sleep disturbance (with the EORTC sleep item) or sleep quality (with the Pittsburgh Sleep Quality Inventory).

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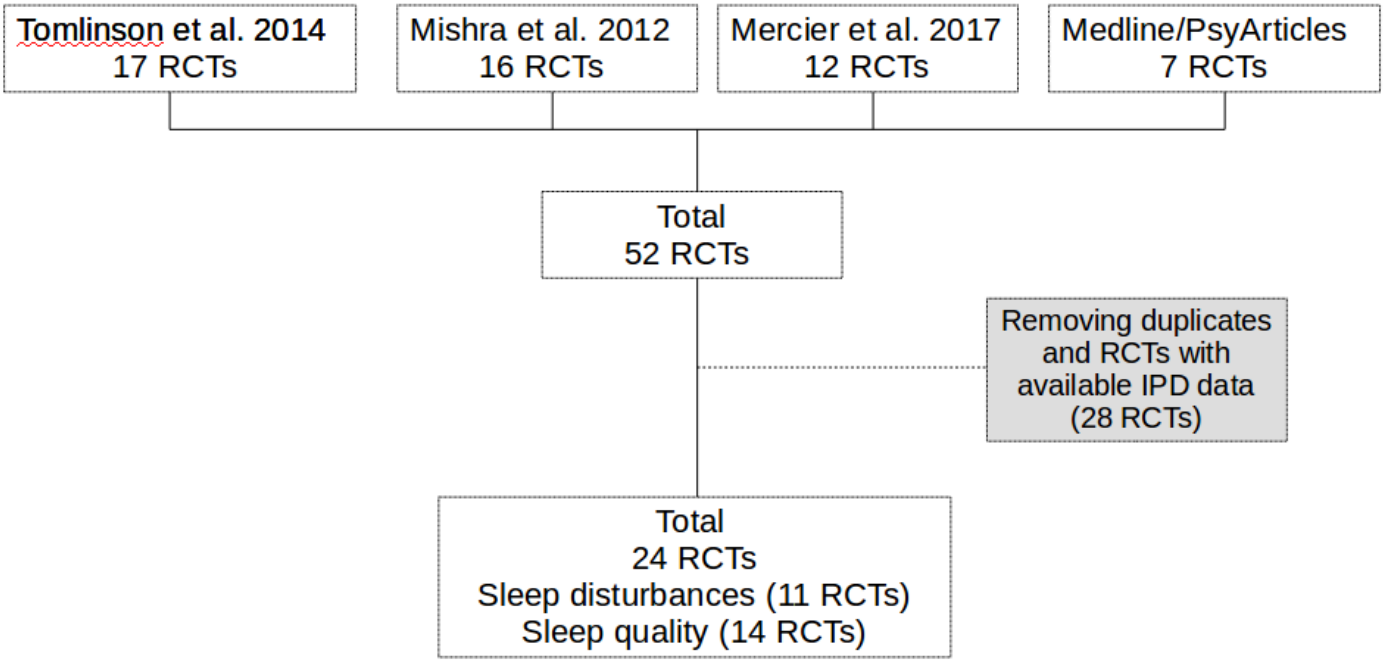
RESULTS

Results from the complementary search literature



Investigations found in database published between 2016 May and 2018 November

Identified RCTs from literature searching

Brown, J. C., Damjanov, N., Courneya, K. S., Troxel, A. B., Zemel, B. S., Rickels, M. R., … Schmitz, K. H. (2018). A randomized dose-response trial of aerobic exercise and health-related quality of life in colon cancer survivors. *Psycho-Oncology*, *27*(4), 1221–1228. https://doi.org/10.1002/pon.4655

Ligibel, J. A., Giobbie-Hurder, A., Shockro, L., Campbell, N., Partridge, A. H., Tolaney, S. M., … Winer, E. P. (2016). Randomized trial of a physical activity intervention in women with metastatic breast cancer: Exercise Intervention in Metastatic Breast Cancer. *Cancer*, *122*(8), 1169–1177.

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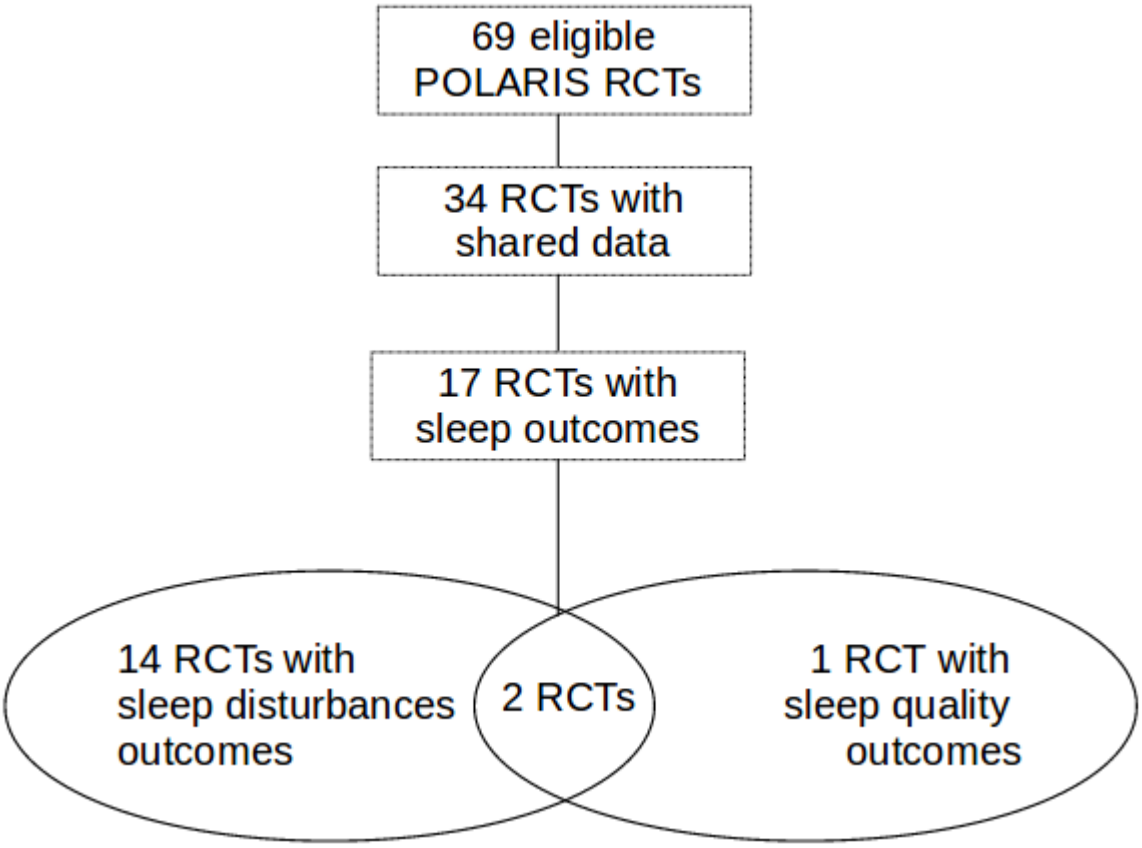
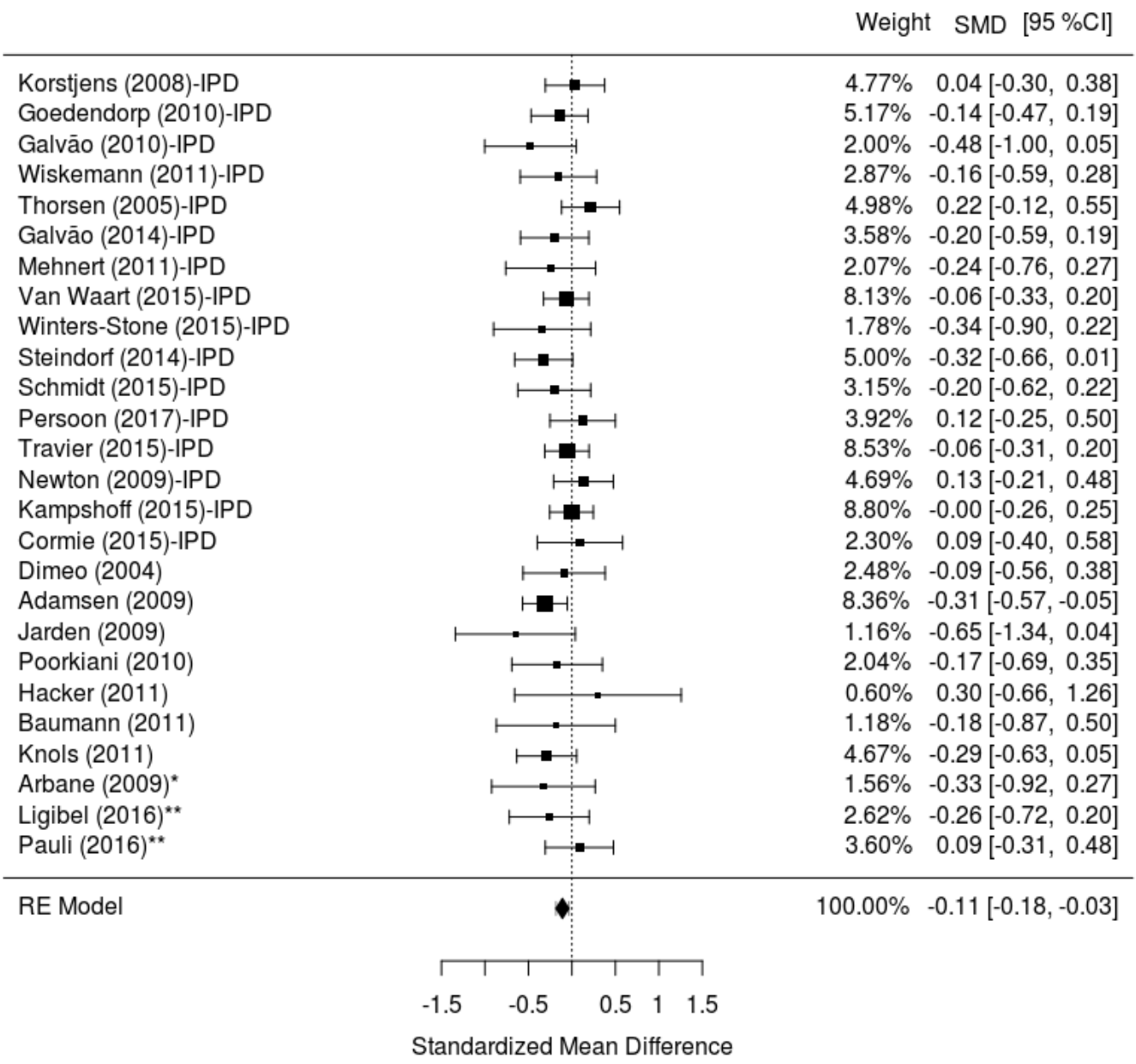
Shobeiri, F., Masoumi, S. Z., Nikravesh, A., Heidari Moghadam, R., & Karami, M. (2016). The Impact of Aerobic Exercise on Quality of Life in Women with Breast Cancer: A Randomized Controlled Trial. *Journal of Research in Health Sciences*, 16(3), 127–132.

Results from POLARIS RCTs with sleep outcomes

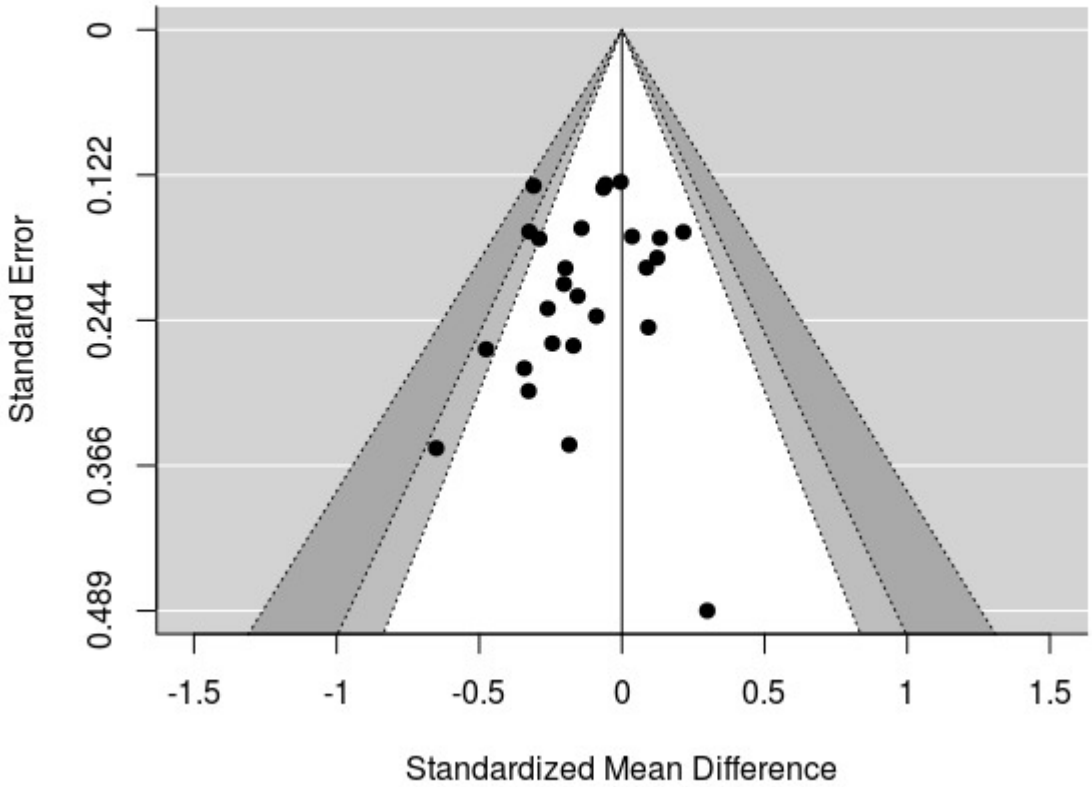


Forest plot including all studies with sleep disturbances data

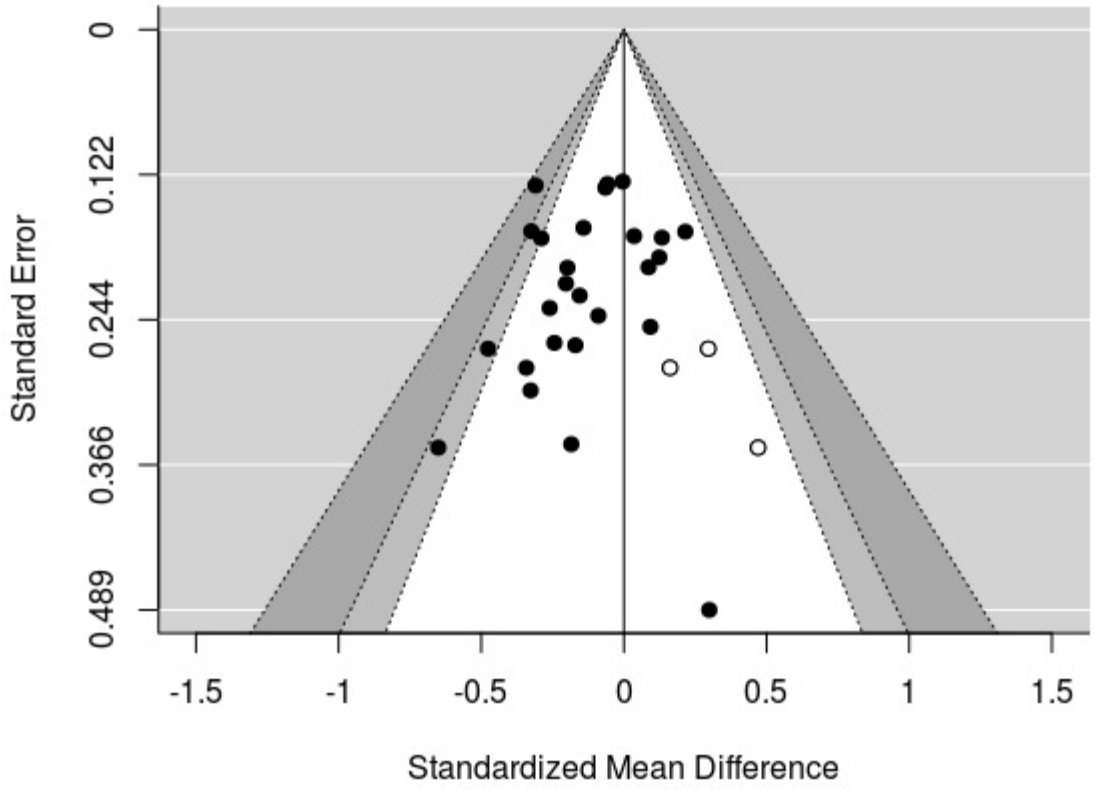


Notes. IPD = Trials with available Individual Participant Data

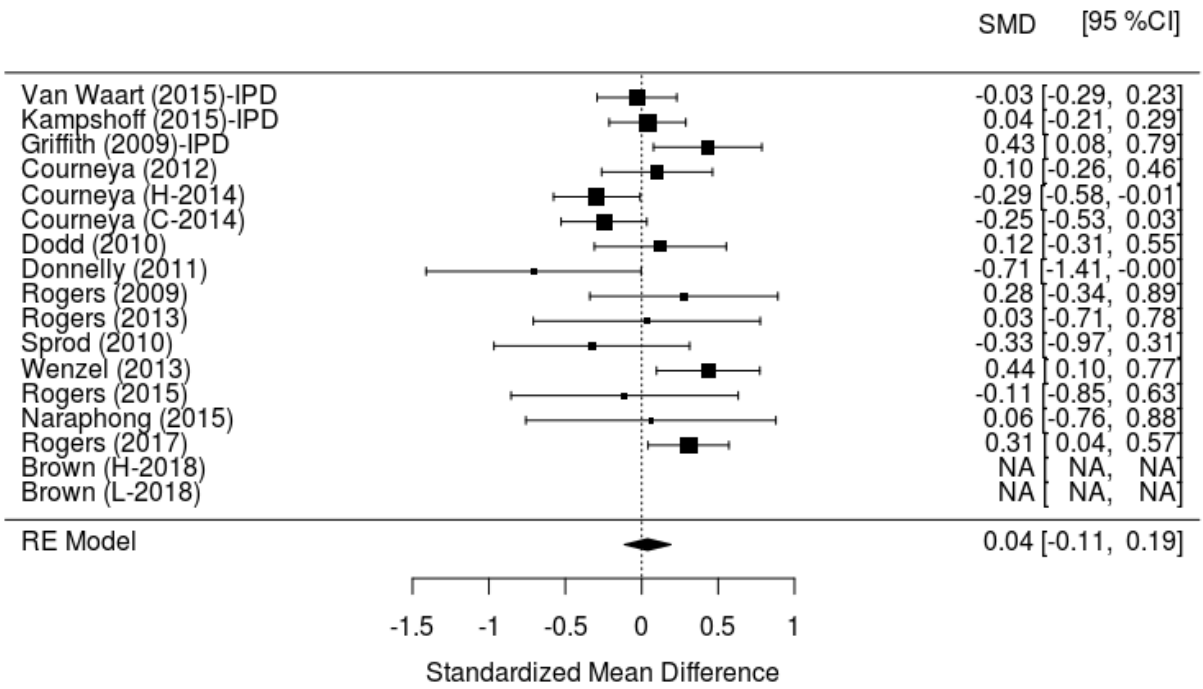
Funnel plot including all studies with sleep disturbances data



Funnel plot including all studies with sleep disturbances data after the fill & trill method



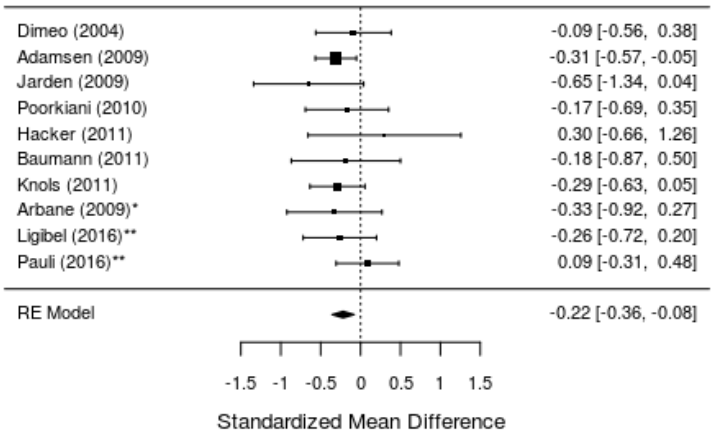
Forest plot including all studies with sleep quality data



Notes. IPD = Trials with available Individual Participant Data

Results from representativeness analyses

Self-reported sleep disturbances
Forest plot for studies without IPD data, excluding one outlier



Sleep Quality

Forest plot for studies without IPD data, excluding two outliers

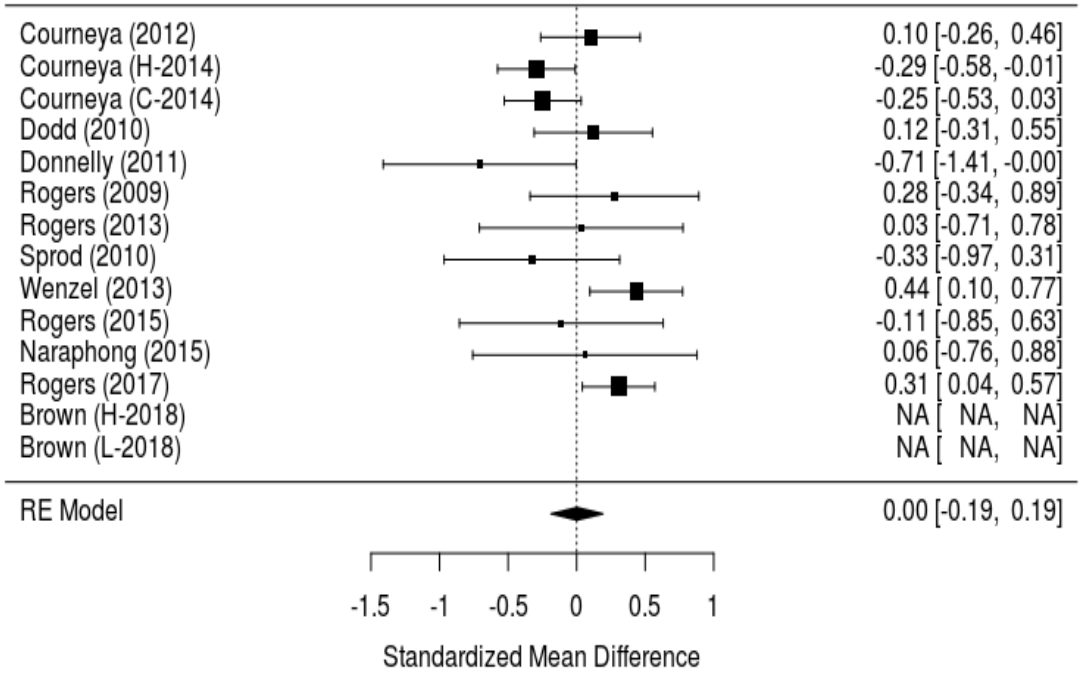


Table S1
Descriptives of studies evaluating the effects of exercise interventions on sleep disturbances and sleep quality

Author (year) *Acronym*	Country	N	Age, mean (SD)	Gender (% female)	Diagnosis	Timing	Delivery mode	Duration (weeks)	FITT		Sleep outcomes	RSG	AC	IO	IR	Adh	Con
Cormie (2015)	AUS	64	67.9 (7.1)	0	Prostate	During ADT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care	S-C30	+	+	+	**-**	?	?
Galvão (2010)	AUS	57	69.8 (7.3)	0	Prostate	During ADT	Supervised	12	F: 2x/week I: moderate T: RE+AE T: 60 min	Usual Care	S-C30	+	+	+	**-**	?	?
Galvão (2014) *RADAR-exercise*	AUS	100	71.7 (6.4)	0	Prostate	Post ADT	Supervised	24	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care with PA brochure	S-C30	+	+	+	**-**	-	?
Goedendorp (2010)	NL	144	57.2 (10.5)	63.2	Mixed	During	Unsupervised	Mean: 31.7	F: towards 5d/week I: ? T: AE T: towards 60 min	Usual care	S-C30	+	+	+	**-**	?	?
Griffith (2009)	USA	126	60.2 (10.6)	38.9	Mixed	During CT, RT or both	Unsupervised	Mean: 12.8	F: 5x/week I: low-moderate T: AE T: 25-35min	Usual care	PSQI	?	?	+	**-**	-	-
Kampshoff (2015) *REACT*	NL	277	53.5 (11.0)	80.1	Mixed	Post	Supervised	12	F: 2x/week I: moderate vs vigorous T: RE+AE T: 60 min	Wait-list	S-C30+ PSQI	+	+	+	**+**	-	+
Korstjens (2008) *OncoRev*	NL	133	50.6 (10.2)	85	Mixed	Post	Supervised	12	F: 2x/week I: AE: moderate-vigorous, RE: low-moderate T: RE+AE T: 120 min	Wait-list	S-C30	+	?	+	**-**	+	?
Newton (2009)	AUS	154	69.0 (9.0)	0	Prostate	During ADT	Supervised	24	F: 2x/week I: moderate-vigorous T: RE+AE vs	Wait-list	S-C30	‡					

									RE+impact T: 60 min								
Persoon (2017)	NL	109	52.4 (11.2)	36.7	Haematological	Post SCT	Supervised	18	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care	S-C30	+	+	+	-	+	-
Schmidt (2015) *BEATE*	GER	88	52.5	10.0	Breast	During CT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE T: 60 min	Relaxation	S-C30 + Sleep duration	+	+	+	+	-	?
Steindorf (2014) *BEST*	GER	141	56.3 (8.9)	100	Breast	During RT	Supervised	12	F: 2x/week I: moderate-vigorous T: RE T: 60 min	Relaxation	S-C30+ Sleep duration	+	+	+	+	-	?
Thorsen (2005)	NOR	139	39.4 (8.3)	67.1	Mixed	Post	Unsupervised	14	F: 2x/week or more I: moderate-vigorous T: RE+AE T: 30 min or more	Usual care	S-C30	+	+	+	-	+	-
Travier (2015); van Vulpen (2015)	NL	237	50.7 (8.8)	100	Breast and Colon	During CT	Supervised	18	F: 2x/week I: moderate-vigorous T: RE+AE T: 60 min	Usual care	S-C30	+	+	+	-	+	?
Van Waart (2015) PACES	NL	253	51.4 (9.5)	95.7	Breast and Colon	During CT	Unsupervised vs supervised	Mean: 15.9	F: supervised: 2x/week; unsupervised towards 5x/week I: supervised: moderate-vigorous Unsupervised: moderate T: supervised: RE+AE; unsupervised: AE T: supervised: 60min; unsupervised: aim 30 min	Usual care	S-C30 +PSQI	+	+	+	+	-	?
Winters-Stone (2015)	USA	51	70.1 (8.6)	0	Prostate	During ADT	Supervised	52	F: 2x/wk supervised (+ 1x/week unsupervised) I: moderate T: RE+impact	Attention control	S-C30	?	?	+	-	+	+

									T: 60 min								
Wiskemann (2011)	GER	80	48.4 (14.4)	31.3	Haematological	Pre-during-post	Supervised	Median exercise: 16.4 Control: 15.7	F: 5x/week I: moderate-vigorous T: RE+AE T: AE: 20-40 min	Attention control	S-C30	+	+	-	-	+	?

*Personal communication with authors. ‡ quality rating could not be performed because papers are not yet published.
ADT= androgen deprivation therapy; AE= Aerobic exercise training; S-C30= Sleep disturbances item from European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; PSQI = Pittsburgh Sleep Quality Inventory; CT= chemotherapy; RE= Resistance exercise training; RT= radiotherapy
Quality assessment: + = high quality; - = low quality; ? = unclear quality; RSG= random sequence generation; AC= allocation concealment; IO=incomplete outcome; IR= incomplete reporting; Adh= adherence; Con= contamination.

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