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REVIEW ARTICLE

Prevalence and risk factors of sleep disturbances in breast cancer survivors: systematic review and meta-analyses

Laurence Leysen[1,2] · Astrid Lahousse[2] · Jo Nijs[1,2,3] · Nele Adriaenssens[2,4] · Olivier Mairesse[5,6] · Sergei Ivakhnov[2] · Thomas Bilterys[1,2,7] · Eveline Van Looveren[1,7] · Roselien Pas[1,2] · David Beckwée[2,8]

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Abstract

Background Breast cancer remains the most frequently diagnosed malignancy among women worldwide, with rising incidence numbers. In Belgium, one out of eight women will be diagnosed with breast cancer. Fortunately, 80% of those breast cancer patients will still be alive 10 years after diagnosis due to improvements in screening and treatment strategies. However, an important portion of the breast cancer survivors (BCS) will face side effects, such as sleep disturbances, long after treatment ends. It has been demonstrated that untreated insomnia in BCS negatively impacts mood, physical symptoms, pain sensitivity, fatigue, and quality of life. Furthermore, insomnia is increasingly considered an independent risk factor for future depression in BCS. The importance of understanding sleep disturbances in cancer populations has been highlighted and recognized as warranting further research. Therefore, the purpose of this systematic review was to determine the prevalence and the risk factors for the development of sleep disturbances in BCS.

Methods PubMed, Web of Science, and PEDro were systematically screened for studies encompassing data regarding the prevalence or risk factors of sleep disturbances in BCS. If possible, meta-analyses were performed. Subgroup analyses were undertaken based on the methodological quality, study design, type of sleep disturbance, and the use of a measurement tool with strong psychometric properties to investigate significant heterogeneity ($I^2 > 50\%$) across studies.

Results A total of 27 studies were found eligible. The pooled estimate for sleep disturbances prevalence is 0.40 (95% confidence interval (CI) = [0.29–0.52], $I^2 = 100\%$, $p < 0.00001$) and ranged from 0.14 (95% CI = [0.04–0.24]) to 0.93 (95% CI = [0.91–0.95]). Subgroup analyses did not reduce the heterogeneity among studies. Meta-analyses were performed for seven risk factors. Significant differences for the odds of developing sleep disturbances were found for hot flashes (pooled OR (OR_p) 2.25, 95% CI = [1.64–3.08], $I^2 = 0\%$, $p = 0.90$), race (OR_p 2.31, 95% CI = [1.56–3.42], $I^2 = 0\%$, $p = 0.47$), and menopause (OR_p 1.84, 95% CI = [1.11–3.06], $I^2 = 0\%$, $p = 0.70$). After withdrawing the studies that did not rely on the use of a measurement tool with strong psychometric properties, pain (OR_p 2.31, 95% CI = [1.36–3.92], $I^2 = 27\%$, $p = 0.25$), depressive symptoms (OR_p 3.20, 95% CI [2.32–4.42], $I^2 = 0\%$, $p = 0.63$), and fatigue (OR_p 2.82, 95% CI = [1.98–4.02], $I^2 = 0\%$, $p = 0.60$) became significant as well, with a substantial decrease of heterogeneity.

Laurence Leysen and Astrid Lahousse share first authorship

✉ David Beckwée
David.beckwee@vub.be

[1] Pain in Motion International Research Group, http://www.paininmotion.be

[2] Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Building F-kine, Laarbeeklaan 103, 1090 Brussels, Belgium

[3] Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Brussels, Belgium

[4] Department of Oncology, University Hospital Brussels, Brussels, Belgium

[5] Experimental and Applied Psychology, Faculty of Psychology and Educational Sciences, Vrije Universiteit Brussel, Brussels, Belgium

[6] Sleep Laboratory and Unit for Chronobiology, Brugmann University Hospital, Brussels, Belgium

[7] Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, Ghent University, Campus Heymans, Building B3, Corneel Heymanslaan 10, 9000 Ghent, Belgium

[8] Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium

Conclusion Prevalence for sleep disturbances ranged from 0.14 to 0.93 with the vast majority of the studies investigating insomnia and sleep-wake disturbances. High heterogeneity makes it difficult to draw firm conclusions. Pain, depressive symptoms, hot flashes, fatigue, non-Caucasian race, and menopausal status were significantly associated with increased odds for developing sleep disturbances.

Keywords Insomnia · Sleep disturbances · Breast cancer survivors · Risk factors · Determinants · Prevalence

Introduction

Rationale

Nowadays, breast cancer remains the most frequent malignancy among women worldwide [1]. Cancer has shown an increase over the past century, with 1 out of 14 women developing breast cancer before the age of 79 years [1].

Early detection and advances in cancer treatment have ensured a 10-year survival in 80% of breast cancer survivors (BCS) in high-income countries [2].

However, disease free does not mean symptom free as a substantial subgroup of BCS will experience troublesome and debilitating symptoms such as sleep disturbances that arise or persist beyond the completion of treatment.

Sleep disturbances encompass various potentially overlapping symptoms and disorders including insomnia, hypersomnia, dyssomnia, excessive daytime sleepiness, circadian rhythm sleep-wake disturbance, sleep apnea, etc. Until now, sleep research in the BCS population was mainly focused on insomnia, which is defined as the predominant complaint of difficulty initiating or maintaining sleep or non-restorative sleep, despite adequate opportunity and circumstances for sleep [3]. In order to diagnose insomnia, the sleep problems must occur at least three nights a week for at least 3 months and give significant rise to distress in work, school, or other daytime functioning [4]. It has been demonstrated that untreated insomnia negatively impacts mood, physical symptoms, pain sensitivity, fatigue, and health-related quality of life [5–7]. Furthermore, insomnia is increasingly viewed as an independent risk factor for developing major depression in BCS [8]. Additionally, insomnia is related to less productivity and increased work absenteeism, leading to high economic expenses [9].

Despite the important implications of sleep disturbances, little empirical work has investigated the factors that might contribute to its development in BCS. In the general population, the following predisposing factors for the development of insomnia have been suggested: sex, increasing hyperarousability, age, and personal and familial history of insomnia [10]. In the context of breast cancer, following factors are associated with an increased risk for insomnia: sick leave, unemployment, widowhood, lumpectomy, chemotherapy, and a less-severe cancer stage at diagnosis [11]. Among breast cancer patients experiencing insomnia symptoms, the risk to meet the diagnostic criteria for insomnia was higher in women who were divorced and had a university degree [11]. However, it is mandatory to discern whether these risk factors are applicable to the BCS population as well since every cancer stage has its own unique set of challenges. BCS will face several psychosocial challenges, including emotional concerns due to persistent physical side effects from illness and treatment, changes in employment, and psychological adjustment to a serious illness [12]. Fear of cancer recurrence, for example, is a significant concern among cancer survivors and associated with higher distress, poorer quality of life, and sleep [13–15]. Besides that, it is hypothesized that the recommendation to rest after cancer treatment in order to compensate post-cancer fatigue might contribute to disturbed sleep and wake cycles [16].

The importance of understanding sleep disturbances in cancer populations has been highlighted [5] and recognized as warranting further research since insomnia remains the most overlooked side effect among BCS [17]. Yet, studies that systematically reviewed the literature regarding the prevalence and risk factors of all sleep disturbances in BCS are currently unavailable.

Objective

Therefore, the purpose of this review was to provide an overview of (1) the prevalence numbers of sleep disturbances in BCS, as well as (2) the investigated risk factors that are related to the development of sleep disturbances in BCS in a systematically manner.

Methods

This systematic review was completed following the PRISMA guidelines [18] and registered in the PROSPERO database (No. CRD42018092893).

Eligibility criteria

To be included, studies needed to meet the following criteria

(1) Subjects needed to meet the definition of a cancer survivor, as suggested by the National Cancer Institute's (NCI) Office of Cancer Survivorship: "A patient with a

history of cancer that is beyond the acute diagnosis and treatment phase" [19]. Since the definition does not involve any specific time criteria, the definition was slightly adjusted: the BCS had to be at least 1 year after diagnosis and 3 months after treatment ending (with exception of hormone and immunotherapy). Furthermore, BCS had to be without any sign of metastasis or recurrence.

(2) Subjects needed to be diagnosed with breast cancer in the past.
(3) There had to be data available to determine the prevalence or the risk factors for the development of sleep disturbances.
(4) Studies needed to be written in English.

The next criteria were applied for exclusion of studies

(1) Study design: literature reviews, case reports, protocol, commentary, and letters.
(2) Subjects that were diagnosed with other cancers besides breast cancer.

Information sources

Articles regarding sleep disturbances in BCS were searched in PubMed, Web of Science, and PEDro. The last search was accomplished in April 2018. Search terms were based on the PECO acronym (population: cancer survivors, exposure: risk factors and prevalence numbers, outcome: sleep disturbances). As our main focus was set on the BCS population, no control group was included. An overview of the applied search terms can be found in Appendix 1. A reverse citation search was performed, and the reference lists of eligible studies were assessed for possible additional citations.

Study selection

After removing duplicates, two reviewers (A.L. and S.I.) independently screened all the titles and abstracts for eligibility in a blinded standardized manner using the Rayyan software [20]. All divergences between the two reviewers were resolved by a third researcher (L.L.). Subsequently, two reviewers (A.L and S.I.) screened the included abstracts full textual.

Data collection process

A data extraction form was created, based on a template provided by the Cochrane Collaboration [21]. Data extraction was performed by two researchers (A.L. and S.I), which was double-checked by a third researcher (L.L.). Any disagreements or problems were resolved by the third researcher (L.L.).

Four authors were contacted to obtain supplementary raw data concerning following predictors: pain, education, age, anxiety, depression, and race [22–25]. Attempts were made by mailing the corresponding, the second and last author. A reminder was sent after 1 month. Both numbers of patients with and without sleep disturbances for each subgroup were requested to make dichotomization possible. None of the four contacted authors [22–25] replied to the request for supplementary raw data. Therefore, these outcomes could not be dichotomized nor added to the meta-analyses.

Quality assessment

Two reviewers (A.L., S.I.) evaluated the methodological quality using an adapted form of the Newcastle-Ottawa Scale (NOS) for cross-sectional studies [26] (Fig. 2). A study with a total score of ≥ 7 out of 10 was considered strong [27]. Any uncertainties were solved by consensus (L.L.).

Summary measures

The primary outcome measures were prevalence numbers of the sleep disturbances and odds ratios (ORs) with a 95% confidence intervals (CIs). The sample size of both the sleep disturbance and non-sleep disturbance subgroups were collected to enable the calculation of OR for each risk factor separately by using the Revman software (Review Manager 5.3.). Subsequently, random effects meta-analyses were performed [28].

Planned methods of analysis

The method proposed by Higgins et al. was used for the assessment of the heterogeneity (I^2) [28]. The I^2 value represents the percentage of variability in effect estimates that can be attributed to heterogeneity rather than sampling error. An $I^2 > 50\%$ is indicative of high heterogeneity [28]. In this case, subgroup analyses were performed to possibly clarify the underlying systematic differences and reduce the substantial heterogeneity. Total NOS-score, study design, the type of sleep disturbance, and the use of a valid measurement tool were taken into account for subgroup analyses. The studies with a total NOS score of ≥ 7 were considered best evidence. Studies that did not attain the NOS score of 7 were excluded from the meta-analyses. Subgroup analyses were performed based on the study design (cross-sectional versus longitudinal study design), the type of sleep disturbance (insomnia versus sleep-wake disturbances + sleep difficulty versus short sleepers versus others) and the use of a valid measurement tool to come to the diagnosis of the sleep disturbance. A Chi-squared (χ^2) test was performed to determine the

significance of the heterogeneity among studies. A conventional p value of 0.05 was used as a cut-off [29].

Additional analyses

The data for the meta-analyses had to be comparable and therefore the following risk factors were dichotomized: pain (pain/no pain) [22, 24, 30, 31], hot flashes (hot flashes/no hot flashes) [22, 25, 31], and race (Caucasian/non-Caucasian) [24, 25].

Results

Study selection

The systematic search resulted in a total of 1101 articles, of which 27 articles (15,620 participants) were finally included [6, 7, 22–25, 30–50] (Fig. 1). The initial inter-rater agreement of the study selection was good (Kappa = 0.90).

Study characteristics

Sample sizes ranged from 26 [7] to 3047 [43]. Twenty-two were cross-sectional studies [6, 7, 22, 23, 25, 31, 32, 34–38, 40, 42–50], and five were cohort studies [24, 30, 33, 39, 41]. Twenty-six studies were conducted in high-income countries [6, 7, 22–25, 30–39, 41–50]. Only one study was performed in a middle-income country (Brazil) [40]. With the exception of hormone and immunotherapy, all BCS had finished their treatment at least 3 months.

Twenty articles retrieved the prevalence of the sleep disturbances by the use of a validated measurement tool [6, 7, 23, 25, 30–32, 34, 35, 37, 38, 40–43, 46–50]. Only four studies provided data on the usage of sleep medication [7, 24, 31, 37].

Different sleep disturbances were retrieved: 11 studies investigated insomnia [22, 23, 30–32, 34, 40, 41, 43–45, 48, 50], 8 studies sleep-wake disturbances [6, 7, 25, 35, 38, 39, 46, 47], and 2 studies short sleepers [24, 33]. Excessive daytime sleepiness [37], sleep difficulty [36], poor sleepers [42], and sleep dysfunction [49] were investigated by only one study (refer to Table 1).

Risk of bias within studies

The overall methodological quality of the included studies is strong [27] with a mean score on the NOS scale of 6.7 ± 1.11 out of 10 and scores ranging from 4 [45, 46] to 8 [7, 22, 24, 25, 31, 33] out of 10 (see Fig. 2). The main weaknesses of the included studies were inappropriate justification of the sample size and not attaining the predetermined response rate of 80%.

Syntheses of results

Prevalence of sleep disturbances in BCS

The prevalence rates of sleep disturbances in BCS ranged from 0.14 (95% CI = [0.04–0.24]) [49] to 0.93 (95% CI = [0.91–0.95]) [37], and the pooled prevalence was 0.40 (95% CI = [0.29–0.52], $I^2 = 100\%$, $p < 0.00001$; 27 studies) (Appendix 2). Results of subgroup analyses can be found in Table 2 (see also Appendixes 3, 4, 5, and 6). None of the subgroup analyses explained the high heterogeneity.

Risk factors for the development of sleep disturbances in BCS

Seven studies reported 27 risk factors for the development of sleep disturbances in BCS [22–25, 30, 31, 40]. The risk factors presented in at least two studies are as follows: pain [22, 24, 30, 31], depression [22, 23, 25, 31], hot flashes [22, 25, 31], fatigue [22, 25, 31], anxiety [22, 31], race [24, 25], and menopause status [24, 25] (Table 3).

Meta-analyses were performed for the risk factors described in more than one article (Appendixes 7, 8, 9, 10, 11, 12, and 13).

Pain (Appendix 7)

Data from four studies ($n = 1907$) [22, 24, 30, 31] were combined, showing that the odds for developing sleep disturbances were significantly higher in patients facing pain complaints compared with pain-free patients (pooled OR (OR_p) 1.68, 95% CI = [1.19–2.37], $I^2 = 55\%$, $p = 0.05$). A subgroup analysis was carried out resulting in an improvement of the heterogeneity ($I^2 = 27\%$, $p = 0.25$) by withdrawing the studies that did not rely on a valid measurement tool [22, 24]. Consequently, OR_p increased to 2.31 (95% CI = [1.36–3.92], $p = 0.002$).

Depressive symptoms (Appendix 8)

Depressive symptoms were approached in four studies ($n = 2487$) [22, 23, 25, 31]. A significant intergroup difference was observed (OR_p 2.54, 95% CI = [1.19–5.44], $p = 0.02$) with significant heterogeneity ($I^2 = 92\%$, $p < 0.00001$). After excluding the only study that did not use a valid measurement tool [22], the heterogeneity dropped to zero ($I^2 = 0\%$, $p = 0.63$) with an increase of the intergroup difference. The odds for the development of sleep disturbances are 3.2 times higher in BCS with depressive symptoms compared with those without depressive symptoms (OR_p 3.20, 95% CI = [2.32–4.42], $p < 0.00001$).

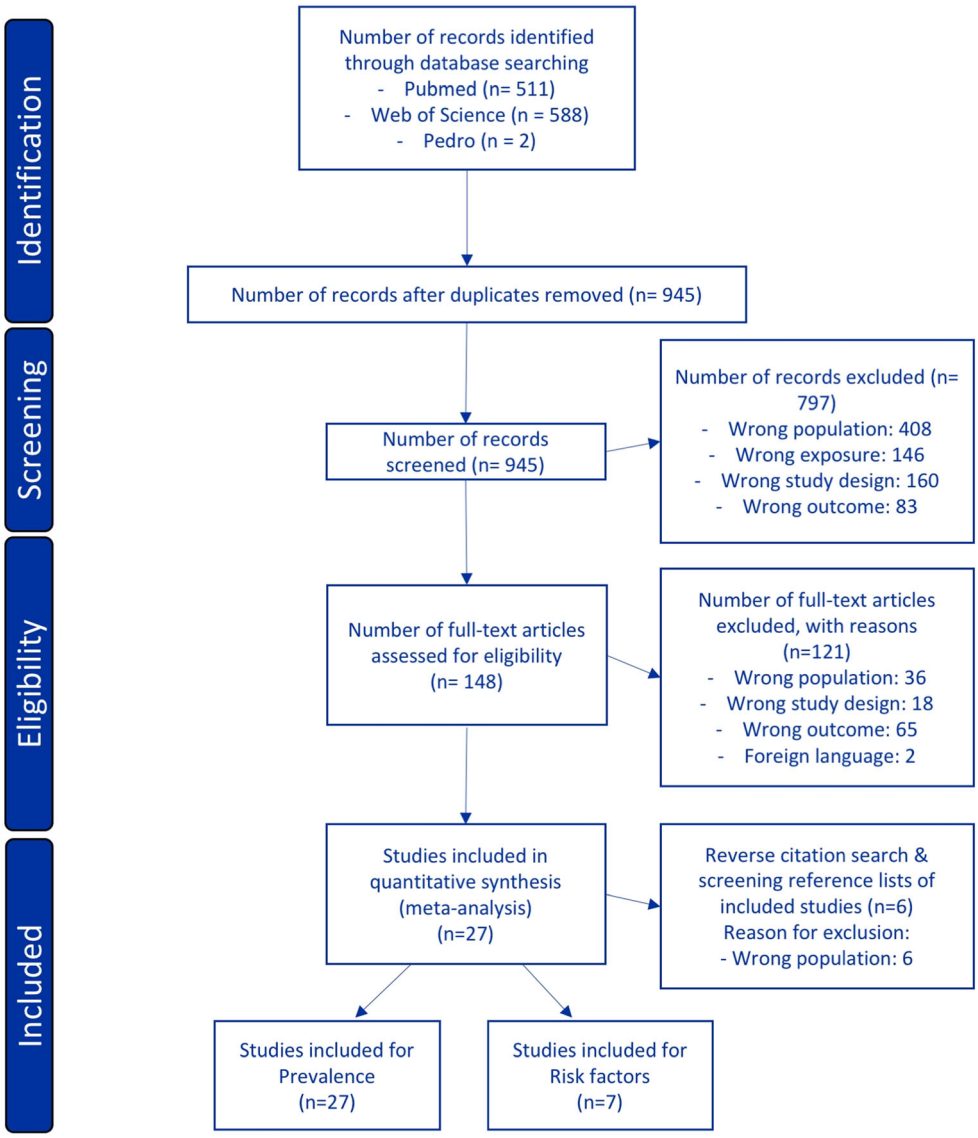

Fig. 1 Flowchart of the study selection process

Hot flashes (Appendix 9)

Hot flashes were studied in three articles ($n = 996$) [22, 25, 31]. After analysis, the odds for developing sleep disturbances were 2.25 times higher in the group with hot flashes (OR_p 2.25, 95% CI = [1.64–3.08], $p < 0.00001$) compared with those who did not suffer from hot flashes. No significant heterogeneity was perceived ($I^2 = 0\%$, $p = 0.90$).

Fatigue (Appendix 10)

For the odds of fatigue, the results of three studies ($n = 2423$) [22, 23, 40] were pooled. No significant association was found between the development of sleep disturbances and fatigue (OR_p 1.90, 95% CI = [0.85–4.26], $p = 0.12$). Given the high heterogeneity ($I^2 = 93\%$, $p < 0.00001$) Dahl et al. was excluded from the meta-analysis due to the fact that they did not rely on a validated measurement tool. Thereafter, no heterogeneity could be observed anymore ($I^2 = 0\%$, $p = 0.60$) and results became significant. BCS with fatigue are 2.82 more likely to develop sleep disturbances in comparison with non-fatigued BCS (OR_p 2.82, 95% CI = [1.98–4.02], $p < 0.00001$).

Anxiety (Appendix 11)

The determinant anxiety was discussed in two studies ($n = 750$) [22, 31]. No significant intergroup difference was observed between BCS facing anxiety complaints and BCS experiencing no anxiety complaints (OR_p 1.37, 95% CI = [0.79–2.38], $p = 0.26$). A significant heterogeneity was found ($I^2 = 70\%$, $p = 0.07$), but given the fact that anxiety was only discussed in two articles, no subgroup analyses could be performed.

Table 1 Prevalence numbers of sleep disturbances in breast cancer survivors

Prevalence

Study	Design	Sample size (*N*)	Age (mean years ± SD) unless otherwise stated	Follow-up (mean ± SD) unless otherwise stated	Sleep outcome	Cut-off	Sleep medication	Type of sleep disturbance	Prevalence of sleep disturbance	Standard error (SE)
Ahn et al. [32], Korea	CS	Total, 1933; BCS, 634; mastectomy, 1299	BCS, 46.6 ± 9.4 years; mastectomy, 47.8 ± 9.2 years	Time since surgery, 50 months (16–143)	EORTC QLQ-C30	NM	NM	Insomnia	23.7% (*N* = 458)	0.01
Alfano et al. [33], USA	C	572	56.5 ± 10.6 years	Time since diagnosis, 30 m (range, 24–41 months)	Study-specific questionnaire	≤ 6 h of sleep	NM	Short sleepers	27.6% (*N* = 158)	0.019
Arraras et al. [34], Spain	CS	243	54.2 ± 6.8 years	Time since diagnosis, 9.8 ± 4.0 years	EORTC QLQ-C30	NM	NM	Insomnia	58.8% (*N* = 143)	0.032
Bao et al. [30], USA	C	Total, 296; CIPN, 173; N-CIPN, 123	62 ± 9.0 years	Time since diagnosis, 6.3 ± 3 years; time since therapy, 5.6 ± 3 years	ISI	ISI, > 7	NM	Insomnia	45.81% (*N* = 136)	0.498
Berger et al. [35], USA	CS	162	58.4 ± 10.7 years	Time since diagnosis, < 5 years, 63; 5–10 years, 68; ≥ 10 years, 31	MDASI	NM	NM	Sleep-wake disturbances	48.8% (*N* = 79)	0.039
Couzi et al. [36], USA	CS	222	54.9 ± 6.1 years	NM	Study-specific questionnaire	NM	NM	Sleep difficulty	44.26% (*N* = 98)	0.033
Dahl et al. [22], Norway	CS	337	54.8 ± 8.5 years; median, 55.3 years at survey (range, 29–75 years)	Time since surgery, 4.0 ± 0.85 years	Study-specific questionnaire	Dichotomous	NM	Insomnia	29.97% (*N* = 101)	0.025
Desai et al. [31], USA	CS	413	61.7 years (range, 33–88 years)	Time since diagnosis, 2–5 years, 132; 5–10 years, 102; ≥ 10 years, 47	ISI	ISI, ≥ 14	7.51% (*N* = 31)	Insomnia	18.64% (*N* = 77)	0.019
Forsythe et al. [37], USA	CS	766	64.30 ± 11.74 years	Time since diagnosis, 2≤	ESS	ESS, > 10	26.2% (missing, 0.5%)	Excessive daytime sleepiness	92.82% (*N* = 711)	0.009
Gonzalez and Lu [38], USA	CS	80	54.25 ± 7.94 years	Time since diagnosis, 19.73 ± 10.44 months (range, 2.60–44.25 months)	PSQI	PSQI, ≥ 5	NM	Sleep-wake disturbances	PSQI score, 66.25% (*N* = 53)	0.053
Heins et al. [39], The Netherlands	C	1256	58.5 ± 13.5 years	Time since diagnosis, 2–5 years	Study-specific questionnaire	NM	NM	Sleep-wake disturbances	6% (*N* = 76)	0.007
Janz et al. [6], USA	CS	1372	60.5 ± 10.7 years	Time since surgery, 7.2 ± 2.5 months	EORTC QLQ-C30	NM	NM	Sleep-wake disturbances	57.1% (*N* = 783)	0.013
Kim et al. [23], Korea	CS	Total, 1933; fatigue group, *N* = 1884	47.4 ± 9.3 years	Time since surgery, 4.6 ± 2.4 years	EORTC QLQ-C30	EORTC QLQ-C30, ≥ 66	NM	Insomnia	Fatigue group, 16.61% (*N* = 313)	0.01
Kluthcovsky et al. [40],	CS		FS, 46.2 ± 8.4 years (range, 35–74 years);	Time since diagnosis, 5.4 ± 4.5 years	EORTC QLQ-C30		NM	Insomnia	35.65% (*N* = 70)	0.033

Table 1 (continued)

Prevalence

Study	Design	Sample size (*N*)	Age (mean years ± SD) unless otherwise stated	Follow-up (mean ± SD) unless otherwise stated	Sleep outcome	Cut-off	Sleep medication	Type of sleep disturbance	Prevalence of sleep disturbance	Standard error (SE)
Brazil		Total, 202; FS, 76; N-FS, 126	N-FS, 51.0 ± 10.6 years (range, 31–85 years)			EORTC QLQ-C30, ≥ 66				
Klyushnenkova et al. [24], USA	C	861	62.0 years (range, 33–95 years)	Time since diagnosis, 7 years	Study-specific questionnaire (sleep duration)	≤ 6 h of sleep	29.3%; sometimes (≤ 4 days/month), 11.3%; often (≥ 5 days/month), 18.0%	Short sleepers	32.7% (*N* = 282)	0.016
Lee et al. [41], Korea	C	205	46.6 ± 10.0 years	Time since diagnosis, 1 year	EORTC QLQ-C30	NM	NM	Insomnia	52.7% (*N* = 108)	0.035
Lowery-Allison et al. [42], USA	CS	200	57 ± 10.0 years	Time since therapy, 63.3 ± 28.8 months	PSQI	PSQI, > 8	*N* = 76 (38%)	Poor sleeper	38% (*N* = 76)	0.034
Marinac et al. [43], USA	CS	3047	82.8 ± 9.0 years	Time since diagnosis, 2 years	IQR	IQR, ≥ 9	NM	Insomnia	46% (*N* = 1402)	0.009
Orre et al. [44], Norway	CS	299	55.2 ± 8.4 years	Time since diagnosis, 4.1 ± 0.9 years (range, 2.7–7.2 years)	Study-specific questionnaire	Dichotomous	NM	Insomnia	30% (*N* = 90)	0.027
Otte et al. [25], USA	CS	246	48.2 ± 8.5 years	Time since diagnosis, 5.6 ± 2.0 months	PSQI	PSQI, > 5	NM	Sleep-wake disturbances	BCS, 65% (*N* = 160)	0.03
Palmer et al. [45], USA	CS	164	55.45 ± 11.97 years	Time since diagnosis, 10.79 ± 4.28 months; time since therapy, 5.17 ± 3.35 months	Study-specific questionnaire (symptoms on scale 0–5)	Symptom present ≥ 1	NM	Insomnia	14.02% (*N* = 23)	0.027
Reinsel et al. [7], USA	CS	26	Moderate/severe (PSQI ≥ 10) 57.9 ± 12.4 years	Moderate/ severe (PSQI ≥ 10); time since therapy, 46.7 ± 27.2 months	PSQ	PSQI, > 10	Moderate/severe (PSQI ≥ 10); 15.38% (*N* = 4)	Sleep-wake disturbance	Moderate/severe (PSQI ≥ 10), 42.31% (*N* = 11)	0.097
Schultz et al. [46], USA	CS	291	Age at diagnosis. 47.8 ± 10 years; age at survey, 66 ± 11 years	Time since diagnosis, 16 ± 8 years	MQOL	NM	NM	Sleep-wake disturbances	90% (*N* = 262)	0.018
Servaes et al. [47], The Netherlands	CS	150	45. 9 ± 6.3 years	Time since diagnosis, 35 ± 17 months; time since therapy, 29 ± 17 months	Groningen Sleep Quality Scale	NM	NM	Sleep-wake disturbances	38% (*N* = 57)	0.04
Taylor et al. [48], USA	CS	51	64.2 ± 12.3 years	Time since diagnosis, 7.2 ± 4.3 years	ISI	ISI, ≥ 8	NM	Insomnia	43.12% (*N* = 22)	0.069
Yang et al. [49], Korea	CS	43	50.1 ± 9.8 years	Time since surgery, 15.4 ± 12.9 months	BCSQ-BC	BCSQ-BS, ≥ 3	NM	Sleep dysfunction	14% (*N* = 13)	0.053
Zucca et al. [50],	CS	249	76.69 ± 20.96 years	Time since diagnosis, > 5 years	EORTC QLQ-C30	NM	NM	Insomnia	17.5% (*N* = 43)	0.024

Table 1 (continued)

Study	Design	Sample size (*N*)	Age (mean years ± SD) unless otherwise stated	Follow-up (mean ± SD) unless otherwise stated	Sleep outcome	Cut-off	Sleep medication	Type of sleep disturbance	Prevalence of sleep disturbance	Standard error (SE)
Prevalence										
Australia										

SD, standard deviation; *BCS*, breast cancer survivors; *NM*, not mentioned; *N*, number; *BCSQ-BC*, brief core set for breast cancer—breast cancer, *CIPN*, chemotherapy-induced peripheral neuropathy; *EORTC*, European organization for research and treatment of cancer; *ESS*, Epworth Sleepiness Scale; *IQR*, interquartile range; *ISI*, insomnia severity index; *MDASI*, M. D. Anderson Symptom Inventory; *MQOL*, McGill Quality-of-Life questionnaire; *PSQI*, Pittsburg sleep quality index; *N-FS*, non-fatigued survivors; *FS*, fatigued survivors; *CS*, cross-sectional; *C*, cohort study

Race (Appendix 12)

Two studies reported on race ($n = 1107$) [24, 25]. The meta-analysis of these results demonstrated that non-Caucasian BCS are 2.31 times more likely to develop sleep disturbances compared with Caucasian BCS (OR_p 2.31, 95% CI = [1.56–3.42], $p < 0.00001$). No significant heterogeneity was observed ($I^2 = 0\%$, $p = 0.47$).

Menopause (Appendix 13)

Same as race, menopause was examined in two studies ($n = 1107$) [24, 25]. The meta-analysis revealed that the odds for the development of sleep disturbances are 1.84 times higher in post-menopausal BCS in comparison with pre-menopausal BCS (OR_p 1.84, 95% CI = [1.11–3.06], $p = 0.02$). No significant heterogeneity was perceived ($I^2 = 0\%$, $p = 0.70$).

Age and education

Since no additional data could be obtained from the respective authors to make accurate dichotomization possible [24, 25], no meta-analyses could be performed for the risk factors age and education.

Others

The remaining risk factors were discussed only in one study: retirement [22], self-rated health [22], hypnotics [22], lymphedema [22], comorbidity [25], income [25], time since diagnosis [31], symptoms [25], impact on life [25], poor physical condition [25], bed partner, and children at home [25]. A detailed overview of these risk factors is presented in Table 3.

Discussion

The purposes of this systematic review and meta-analyses were first to investigate the prevalence of sleep disturbances among BCS and secondly to identify factors that could be responsible for the development of the sleep disturbances. A total of 27 studies were included which together provided 27 prevalence numbers and 21 risk factors for the development of sleep disturbances. We acknowledge that there are a multitude of sleep disturbances, of which the vast majority of the publications included in this study only assessed for insomnia and sleep-wake disturbances. The prevalence numbers ranged from 0.14 to 0.93 with a pooled estimate of 0.40. However, the heterogeneity across the studies was very high and very little change could be obtained after subgroup analyses. For seven risk factors, it was possible to carry out a meta-analysis. Three out of seven examined factors (hot flashes, non-Caucasian race, and post-menopausal status) demonstrated

Fig. 2 Quality assessment by the NOS checklist

Studies	Selection				Comparibility	Outcome		Total
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure	Confounding factors	Assessment of the outcom	Statistical test	Mean = 6.7 Median= 7
Ahn et al. (2006)	★			★★	★★	★	★	7
Alfano et al. (2011)	★		★	★★	★★	★	★	8
Arraras et al. (2016)	★			★★	★	★	★	6
Bao et al. (2016)*	★		★	★★	★	★	★	7
Berger et al. (2011)	★		★	★	★★	★	★	7
Couzi et al. (1995)	★			★★	★	★★	★	7
Dahl et al. (2011)	★	★	★	★	★★	★	★	8
Desai et al. (2013)	★		★	★★	★★	★	★	8
Forsythe et al. (2012)	★			★★	★★	★	★	7
Gonzalez et al. (2017)	★			★★	★★	★	★	7
Heins et al. (2012)*	★				★	★★	★	5
Janz et al. (2007)	★			★★	★★	★	★	7
Kim et al. (2007)	★		★	★	★★	★	★	7
Kluthcovsky et al. (2011)	★		★	★	★★	★	★	7
Klyushnenkova et al. (2015)*	★		★	★★	★★	★	★	8
Lee et al. (2011)*	★			★★	★★	★	★	7
Lowerry-Allison et al. (2017)	★		★	★★	★	★		6
Marinac et al. (2017)			★	★★	★★	★	★	7
Orre et al. (2011)	★			★★	★★	★	★	7
Otte et al. (2010)	★	★		★★	★★	★	★	8
Palmer et al. (2016)	★			★		★	★	4
Reinsel et al. (2015)	★		★	★★	★★	★	★	8
Schultz et al. (2005)	★			★		★	★	4
Servaes et al. (2001)	★			★	★★	★		5
Taylor et al. (2011)				★★	★★	★	★	6
Yang et al. (2012)	★			★★	★★	★	★	7
Zucca et al. (2011)	★			★★	★★	★	★	7

to be significantly associated with an elevated chance for the development of sleep disturbances in BCS. After applying subgroup analyses for the meta-analyses that demonstrated a high heterogeneity, pain, depressive symptoms, and fatigue became significant as well. The remaining risk factor anxiety was not significantly related to the development of sleep disturbances in BCS.

After years of cancer and sleep research, we must come to the conclusion that it was not possible to provide a proper image of the prevalence of sleep disturbances among BCS, due to the significant heterogeneity of the pooled estimate ($I^2 = 100\%$). A broad spectrum of reasons can be held accountable for the discrepancies in mapping the prevalence of sleep disturbances in BCS. First of all, the importance of following and applying the correct nosology and criteria of the *International Classification of Sleep Disorders (Third Edition)* to come to the diagnosis of sleep disturbances should be emphasized [51].

Second, an important portion of the included studies relied on the EORTC QLQ C30 for the diagnosis of sleep disturbances. However, this measurement tool is only validated to measure quality of life in patients and may not be appropriate for the diagnosis of sleep disturbances. Fiorentino et al. [52] for example, tried to reflect the current state and found that,

Table 2 Overview of the subgroup analyses for the prevalence of sleep disturbances in breast cancer survivors

Subgroup	No. of studies	Prevalence [95% CI]	I^2 (%)	*p* value
All studies	27	0.40 [0.29–0.52]	100	< 0.00001
Study quality				
NOS ≥ 7 (ref)	20	0.40 [0.28–0.53]	100	< 0.00001
NOS < 7	7	0.37 [0.09–0.64]	100	< 0.00001
Study design				
LS	5	0.30 [0.12–0.48]	99	< 0.00001
CS	22	0.42 [0.30–0.55]	100	< 0.00001
Type of sleep disturbance				
Sleep-wake disturbance + sleep difficulty	9	0.51 [0.25–0.77]	100	< 0.00001
Insomnia	11	0.33 [0.25–0.42]	98	< 0.00001
Short sleepers	2	0.30 [0.25–0.35]	76	0.04
Measurement tool				
Only study-specific questionnaire	7	0.31 [0.16–0.45]	99	< 0.00001
Validated measurement tool	20	0.44 [0.30–0.57]	100	< 0.00001

Table 3 Risk factors for the development of sleep disturbances in breast cancer survivors

Study	Design	Sample size (*N*)	Age (mean years ± SD) unless otherwise stated	Follow-up (mean ± SD) unless otherwise stated	Sleep outcome	Cut-off	Sleep medication
Pain							
Bao et al. [30], USA	C	Total, 296; CIPN, 173; N-CIPN, 123	62 ± 9.0 years	Time since diagnosis, 6.3 ± 3 years; time since therapy, 5.6 ± 3 years	ISI	ISI, > 7	NM
Dahl et al. [22], Norway	CS	337	54.8 ± 8.5 years; median, 55.3 years at survey (range: 29–75 years)	Time since surgery: 4.0 ± 0.85 years	Study specific questionnaire	Dichotomous	NM
Desai et al. [31], USA	CS	413	61.7 years (range, 33–88 years)	Time since diagnosis—2–5 years, 132; 5–10 years, 102; ≥ 10 years, 47	ISI	ISI, ≥ 14	7.51% (*N* = 31)
Klyushnenkova et al. [24], USA	C	861	62.0 years (range, 33–95 years)	Time since diagnosis, 7 years	Study-specific questionnaire (sleep duration)	≤ 6 h of sleep	29.3%: sometimes (≤ 4 days/month), 11.3%; often (≥ 5 days/month), 18.0%
Hot flashes							
Dahl et al. [22], Norway	CS	337	54.8 ± 8.5 years; median, 55.3 years at survey (range, 29–75 years)	Time since surgery, 4.0 ± 0.85 years	Study-specific questionnaire	Dichotomous	NM
Desai et al. [31], USA	CS	413	61.7 years (range, 33–88 years)	Time since diagnosis—2–5 years, 132; 5–10 years, 102; ≥ 10 years, 47	ISI	ISI, ≥ 14	7.51% (*N* = 31)
Otte et al. [25], USA	CS	246	48.2 ± 8.5 years	Time since diagnosis, 5.6 ± 2.0 months	PSQI	PSQI, > 5	NM
Depressive symptoms							
Dahl et al. [22], Norway	CS	337	54.8 ± 8.5 years; median, 55.3 years at survey (range, 29–75 years)	Time since surgery, 4.0 ± 0.85 years	Study-specific questionnaire	Dichotomous	NM
Desai et al. [31], USA	CS	413	61.7 years (range, 33–88 years)	Time since diagnosis—2–5 years, 132; 5–10 years, 102; ≥ 10 years, 47	ISI	ISI, ≥ 14	7.51% (*N* = 31)
Kim et al. [23], Korea	CS	Total, 1933; fatigue group, *N* = 1884	47.4 ± 9.3 years	Time since surgery, 4.6 ± 2.4 years	EORTC QLQ-C30	EORTC QLQ-C30, ≥ 66	NM
Otte et al. [25], USA	CS	246	48.2 ± 8.5 years	Time since diagnosis, 5.6 ± 2.0 months	PSQI	PSQI, > 5	NM
Fatigue							
Dahl et al. [22], Norway	CS	337	54.8 ± 8.5 years; median, 55.3 years at survey (range, 29–75 years)	Time since surgery, 4.0 ± 0.85 years	Study-specific questionnaire	Dichotomous	NM

Table 3 (continued)

Kim et al. [23], Korea	CS	Total, 1933; fatigue group, $N = 1884$	47.4 ± 9.3 years	Time since surgery, 4.6 ± 2.4 years	EORTC QLQ-C30	EORTC QLQ-C30, ≥ 66	NM
Kluthcovsky et al. [40], Brazil	CS	Total, 202; FS, 76; N-FS, 126	FS, 46.2 ± 8.4 years (range, 35–74 years); N-FS, 51.0 ± 10.6 years (range, 31–85 years)	Time since diagnosis, 5.4 ± 4.5 years	EORTC QLQ-C30	EORTC QLQ-C30, ≥ 66	NM
Anxiety							
Dahl et al. [22], Norway	CS	337	54.8 ± 8.5 years; median, 55.3 years at survey (range, 29–75 years)	Time since surgery, 4.0 ± 0.85 years	Study-specific questionnaire	Dichotomous	NM
Desai et al. [31], USA	CS	413	61.7 years (range, 33–88 years)	Time since diagnosis—2–5 years, 132; 5–10 years, 102; ≥ 10 years, 47	ISI	ISI, ≥ 14	7.51% ($N = 31$)
Race							
Klyushnenkova et al. [24], USA	C	861	62.0 years (range, 33–95 years)	Time since diagnosis, 7 years	Study-specific questionnaire (sleep duration)	≤ 6 h of sleep	29.3%: sometimes (≤ 4 days/month), 11.3%; often (≥ 5 days/month), 18.0%
Otte et al. [25], USA	CS	246	48.2 ± 8.5 years	Time since diagnosis, 5.6 ± 2.0 months	PSQI	PSQI, > 5	NM
Post-menopause							
Klyushnenkova et al. [24], USA	C	861	62.0 years (range, 33–95 years)	Time since diagnosis, 7 years	Study-specific questionnaire (sleep duration)	≤ 6 h of sleep	29.3%: sometimes (≤ 4 days/month), 11.3%; often (≥ 5 days/month), 18.0%
Otte et al. [25], USA	CS	246	48.2 ± 8.5 years	Time since diagnosis, 5.6 ± 2.0 months	PSQI	PSQI, > 5	NM
Others							
Dahl et al. [22], Norway	CS	337	54.8 ± 8.5 years; median, 55.3 years at survey (range, 29–75 years)	Time since surgery, 4.0 ± 0.85 years	Study-specific questionnaire	Dichotomous	NM
Desai et al. [31], USA	CS	413	61.7 years (range, 33–88 years)	Time since diagnosis—2–5 years, 132; 5–10 years, 102; ≥ 10 years, 47	ISI	ISI, ≥ 14	7.51% ($N = 31$)
Otte et al. [25], USA	CS	246	48.2 ± 8.5 years	Time since diagnosis, 5.6 ± 2.0 months	PSQI	PSQI, > 5	NM

Study	Type of sleep disturbance	Prevalence of sleep disturbance	Risk factor variable	PE (n)	(Adjusted) OR (95% CI)	Significance (p value)
Pain						
Bao et al. [30], USA	Insomnia	45.81% ($N = 136$)	Insomnia: - No CIPN - CIPN No insomnia: - No CIPN	134 43 91 162 80	OR, 2.06 [1.28–3.32]	0.0028

Table 3 (continued)

			- CIPN	82		
Dahl et al. [22], Norway	Insomnia	29.97% ($N = 101$)	Arm/shoulder pain	NM		
			No			
			Yes		OR_{Adj}[a]: 1.05 [0.98–1.11] [MA]	0.76
Desai et al. [31], USA	Insomnia	18.64% ($N = 77$)	Joint pain	NM		
			No (ref)			
			Yes			
			- moderate/ moderate		OR_{Adj}[b], 1.53 [0.55–4.26][MA]	0.41
			- Severe		OR_{Adj}[b], 4.84 [1.71–13.69][MA]	0.003
Klyushnenkova et al. [24], USA	Short sleepers	32.7% ($N = 282$)	Acute pain			
			No (Ref)	269		
			Yes			
			- Mild/ moderate	387	OR_{Adj}[f], 1.15 [0.80–1.65][MA]	0.01
			- Severe	192	OR_{Adj}[f], 1.99 [1.31–3.03][MA]	0.0013
Hot flashes						
Dahl et al. [22], Norway	Insomnia	29.97% ($N = 101$)	No (ref)	NM		
			Yes		OR_{Adj}[a], 1.92 [1.09–3.37][MA]	0.02
Desai et al. [31], USA	Insomnia	18.64% ($N = 77$)	No (ref)	NM		
			Yes			
			- Mild/ moderate		OR_{Adj}[b], 2.28 [1.13–4.60][MA]	0.022
			- Severe		OR_{Adj}[b], 2.29 [1.23–6.81][MA]	0.015
Otte et al. [25], USA	Sleep-wake disturbances	BCS, 65% ($N = 160$)	No (ref)	NM		
			Yes		OR_{Adj}[d], 2.68 [1.41–5.00][MA]	< 0.05
Depressive symptoms						
Dahl et al. [22], Norway	Insomnia	29.97% ($N = 101$)	No (ref)	NM		
			Yes		OR_{Adj}[a], 1.13 [1.05–1.21][MA]	0.001
Desai et al. [31], USA	Insomnia	18.64% ($N = 77$)	No (ref)	NM		
			Yes		OR_{Adj}[b], 3.57 [1.48–8.52][MA]	0.004
Kim et al. [23], Korea	Insomnia	Fatigue group, 16.61% ($N = 313$)	No (ref)	1119		
			Yes	372	OR_{adj}[c], 2.94 [2.02–4.24][MA]	< 0.0001
Otte et al. [25], USA	Sleep-wake disturbances	BCS, 65% ($N = 160$)	No (ref)	NM		
			Yes		OR_{Adj}[d], 4.62 [1.91–11.78][MA]	< 0.05
Fatigue						
Dahl et al. [22], Norway	Insomnia	29.97% ($N = 101$)	No (ref)	NM		
			Yes		OR_{Adj}[a], 1.05 [0.98–1.11][MA]	0.16

Table 3 (continued)

Kim et al. [23], Korea	Insomnia	Fatigue group, 16.61% ($N = 313$)	No (ref)	NM		
			Yes		OR_{Adj}[c], 2.98 [1.98–4.49][MA]	< 0.0001
Kluthcovsky et al. [40], Brazil	Insomnia	35.65% ($N = 70$)	No (ref)	126	OR_{Adj}[e], 2.40 [1.19–4.86][MA]	0.015
			Yes	67		
Anxiety						
Dahl et al. [22], Norway	Insomnia	29.97% ($N = 101$)	No (ref)	NM		
			Yes		OR_{Adj}[a], 1.11 [0.99–1.24][MA]	0.07
Desai et al. [31], USA	Insomnia	18.64% (N = 77)	No (ref)	NM		
			Yes		OR_{Adj}[b], 1.99 [1.08–3.65][MA]	0.027
Race						
Klyushnenkova et al. [24], USA	Short sleepers	32.7% ($N = 282$)	Caucasian (ref)	716		
			Non-Caucasian	199	OR_{Adj}[f], 2.16 [1.40–3.35][MA]	< 0.01
Otte et al. [25], USA	Sleep-wake disturbances	BCS, 65% ($N = 160$)	Caucasian (ref)	NM		
			Non-Caucasian		OR_{Adj}[d], 3.14 [1.26–7.83][MA]	< 0.05
Post-menopause						
Klyushnenkova et al. [24], USA	Short sleepers	32.7% ($N = 282$)	No (ref)	60		
			Yes	794	OR_{Adj}[f], 2.05 [0.97–4.38][MA]	0.18
Otte et al. [25], USA	Sleep-wake disturbances	BCS, 65% ($N = 160$)	No (ref)	NM		
			Yes		OR_{Adj}[d], 1.68 [0.84–3.33][MA]	< 0.00
Others						
Dahl et al. [22], Norway	Insomnia	29.97% ($N = 101$)	Not on disability pension (ref)	229	OR_{Adj}[a], 0.96 [0.50–1.82]	0.89
			- No insomnia	172		
			- Insomnia	57		
			On disability pension	108		
			- No Insomnia	64		
			- Insomnia	44		
			Poor self-rated health (ref)	95	OR_{Adj}[a], 0.75 [0.35–1.57]	0.44
			- No Insomnia	52		
			- Insomnia	42		
			Good self-rated health	240		
			-No Insomnia	182		
			-Insomnia	58		
			SF-36 PCS score		OR_{Adj}[a], 0.98 [0.94–1.01]	0.17
			No use of analgesics (ref)	281	OR_{Adj}[a], 1.74 [0.79–3.83]	0.17
			-No Insomnia	212		

Table 3 (continued)

			-Insomnia	69		
			Regular use of analgesics	56		
			-No Insomnia	24		
			-Insomnia	32		
			No use of hypnotics (ref)	228	OR_{Adj}[a], 7.92 [3.40–18.43]	0.001
			-No Insomnia	223		
			-Insomnia	65		
			Regular use of hypnotics	49		
			-No Insomnia	13		
			-Insomnia	36		
			Lymphedema			
			No (ref.)	266	OR_{Adj}[a], 1.04 [0.51–2.11]	0.92
			-No Insomnia	197		
			-Insomnia	69		
			Yes:	71		
			-No Insomnia	39		
			-Insomnia	32		
Desai et al. [31], USA	Insomnia	18.64% (N = 77)	Time since BC diagnosis			
			- < 2 years (ref)			
			- 2–5 years		OR_{Adj}[b], 1.94 [1.02–3.69]	0.045
			- > 5 years		OR_{Adj}[b], 1.20 [0.62–2.34]	0.583
			Education			
			- Graduate/profession (ref)			
			- High school or less		OR_{Adj}[b], 1.21 [0.61–2.33]	0.57
			- College		OR_{Adj}[b], 0.52 [0.24–1.11]	0.09
			Age, years			
			- > 65 (ref)			
			- 55–65		OR_{Adj}[b], 1.88 [0.98–3.59]	0.056
			- < 55		OR_{Adj}[b], 2.31 [1.11–4.81]	0.026
Otte et al. [25], USA	Sleep-wake disturbances	BCS, 65% (*N* = 160)	High income over $50,000/year (ref)	NM		
			Low income under $50,000/year		OR_{Adj}[d], 1.49 [0.70–3.20]	< 0.00
			1 comorbidity or less (ref)			
			2/more comorbidities		OR_{Adj}[d], 0.91 [0.18–4.69]	< 0.00
			Poor physical functioning (ref)			
			Physical functioning		OR_{Adj}[d], 2.5 [1.12–5.86]	< 0.05

Table 3 (continued)

Symptoms		
- # = 0–5	OR_{Adj}[d], 1.43 [0.61–3.33]	< 0.00
- # = 6 and above	OR_{Adj}[d], 1.30 [0.52–3.26]	< 0.00
Impact of a life event		
- Mean score = 1–2	OR_{Adj}[d], 2.06 [0.52–8.11]	< 0.00
- Mean score = 3 or more	OR_{Adj}[d], 2.77 [0.48–16.10]	< 0.00
- No bed partner (ref)		
- Having bed partner	OR_{Adj}[d], 1.56 [0.70–3.46]	< 0.00
No children in home (ref)		
Children in home	OR_{Adj}[d], 0.59 [0.32–1.11]	< 0.00

SD, standard deviation; *PE*, patients exposed; *OR*, odds ratio; *CI*, confidence interval; *BCS*, breast cancer survivors; *NM*, not mentioned; *N*, number; *CIPN*, chemotherapy-induced peripheral neuropathy; *EORTC*, European organization for research and treatment of cancer; *ESS*, Epworth Sleepiness Scale; *ISI*, insomnia severity index; *NS*, night sweat; *PSQI*, Pittsburg Sleep Quality Index; *CS*, cross-sectional; *C*, cohort; *N-FS*, non-fatigued survivors; *FS*, fatigued survivors

[a] Adjusted for level of education, on disability pension and menopausal status

[b] Adjusted for age, education level, and time since diagnosis

[c] Adjusted for financial difficulties, systemic side effects, and upset by hair loss

[d] Adjusted for race and menopausal status

[e] Boneferroni correction: adjusted for sociodemographic, clinical, and symptom variables identifies some variables with p values lower than 0.05 and age at interview, age at diagnosis, pain, dyspnea, insomnia, constipation, and appetite loss

[f] Adjusted for age, race, presence of acute pain, education level, and menopausal status

he prevalence for insomnia ranged from 20 to 70% in BCS, depending on the study design and their method of assessment [52].

Third, as most of the included studies were cross-sectional, the presence of sleep disturbances before cancer diagnosis was neglected, possibly leading to an underestimation of the prevalence numbers as it is known that aggravation of sleep problems can occur after cancer diagnosis [53].

Last, there is the relatively high difference in age among the included BCS which might be responsible for the significant heterogeneity. Currently, the existing evidence on the association between age and sleep disturbances is conflicting. While some demonstrated poorer sleep in younger women [54], others claim age not to be related to poorer sleep quality [42]. Some of the included studies tried to subdivide their population in a younger and older category based on their menopausal status or age. However, the literature has no strict formulated cut-off provided for this partition in BCS. Moreover, we tried to confirm possible age-involvement for insomnia in BCS, but there was insufficient data to do so.

In the future, studies should not only rely on the International Classification of Sleep Disorders but also use measurement tools that are validated to measure sleep disturbances and disorders. Furthermore, more longitudinal designs are needed to provide a better insight in whether the sleep disturbances were already existing premorbid and aggravated by the cancer, or whether the cancer treatment was the main reason for the sleep disturbances. Lastly, the relationship between sleep patterns and age needs to be clarified, potentially by dichotomizing participants into younger and older age categories.

The secondary goal in this review was to describe the risk factors for the development of sleep disturbances. The results of our study are in concordance with a previous review, in which psychological factors such as depressive symptoms and anxiety were related to an increased chance of insomnia [55]. However, the exact etiological relationship between sleep disturbances, anxiety and depression remains unclear. Some studies demonstrated a bidirectional relationship, suggesting that each problem contributes to the development and is a consequence of one another [56, 57]. Other studies found two distinct cause-effect associations, in which anxiety predicts a sleep disturbance and a sleep disturbance predicts depression but not vice versa [58, 59]. It should be emphasized that this research was performed in a non-cancer population. To draw firm conclusions, further research in BCS is needed to understand the etiological relationship between sleep disturbances, anxiety and depression. What is known in cancer research up to now is that the association between anxiety and insomnia in BCS might be explained by the presence of fear of recurrence [60]. Furthermore, it has been demonstrated that resolving insomnia reduces depressive symptoms and anxiety, which reinforces the belief that insomnia is the key risk factor for psychopathology [61]. Nevertheless, targeting the depressive symptoms should form a cornerstone in the treatment plan as it is proven that depressed patients are less likely to adhere to the cancer therapy recommendations, show a poorer understanding of treatment recommendations, and heightened anxiety levels [62].

Pain has been postulated as another associated factor in the development of sleep disturbances, which was confirmed in this review. Forsythe et al. reported that about 30% of the BCS are confronted with pain which can last up to 10 years after the treatment ending [63]. However, a moderate heterogeneity was present, which might be explained by pooling all different types of pain together (e.g., joint pain, shoulder/arm pain, and chemotherapy-induced peripheral neuropathy (CIPN)). The association between CIPN and increased anxiety, depression, and insomnia levels in BCS was demonstrated previously [30]. Furthermore, it has been shown that women taking aromatase inhibitors are more likely to develop joint pain, resulting in difficulties to fall asleep or remain asleep [31].

Most breast cancer patients are diagnosed in their midlife stage, with 25% of the women being premenopausal [64]. Due to the chemotherapy and hormone therapy, a decrease in estrogen levels and sudden onset of vasomotor symptoms occurs, leading to an earlier transition to the post-menopausal stage [65]. This transition goes hand-in-hand with the development of hot flashes in about 75% of all menopausal women [66]. Despite the fact that our study showed a significant association between hot flashes and insomnia, no confirmation could be found for the fact that the post-menopausal status might make the BCS more susceptible to the development of sleep disturbances. Hot flashes and nocturnal diaphoresis can cause sleep disturbances in both menopausal healthy women and menopausal breast cancer patients. However, they tend to be more frequent [67], more severe, and more persistent [68], as evidenced by a linear association between the severity of the hot flashes and the prevalence of sleep disturbances in BCS [36].

Our study demonstrated that fatigue is a risk factor for the development of sleep disturbances, which was confirmed by a recent review [69]. Strong evidence was found for the relationship between higher fatigue levels and sleep disturbances. One should be aware that this relationship was mainly demonstrated for insomnia

and not the other types of sleep disturbances. Besides that, the results were extracted from mainly cross-sectional studies making it impossible to draw conclusions regarding the direction [69]. However, one study in BCS found that fatigue did not predict poorer sleep, but poorer sleep significantly predicted higher levels of fatigue the next day [70]. These findings suggest that fatigue is rather a secondary problem of sleep disturbances. Overall, little is known about the underlying mechanism and directionality of fatigue, making further research warranted [69].

Race was the final significant risk factor, with non-Caucasian BCS being more susceptible for the development of sleep disturbances. Despite the fact that research regarding racial differences in sleep medicine is still in its infancy, a few findings might explain our results. Previous research demonstrated elevated prevalence numbers of obstructive sleep apnea among Black, Hispanic, and Native Americans, most likely due to the higher levels of obesity found in these groups [71]. Furthermore, it is proven that racial discrimination, which is experienced by almost all minority groups, is not only a chronic stressor but also has significant associations with complaints of sleep disturbances [72]. Perceived discrimination in healthcare settings was associated with poorer self-reported sleep quality, greater daytime sleepiness, shorter sleep duration, poorer sleep efficiency, and a shorter time period spent in REM sleep [72]. However, more research is needed in order to obtain a more complete picture of the interracial sleep differences in BCS [73].

Strengths and limitations

This study should be considered in light of some strengths and limitations. To our knowledge, this was the first study that performed a review in a systematically matter to obtain an initial estimate of the prevalence and risk factors for the development of sleep disturbances among the BCS. By complying to PRISMA guidelines, meta-analyses and subgroup analyses, a rigorous methodology could be achieved.

Despite the innovative aspect of the study, a few limitations should be acknowledged as well. First, two studies were excluded due to language restrictions and might have increased the risk on influencing our estimates in both the risk factors as well as the prevalence. However, a study by Jüne et al. showed that generally little effect on the estimates was deemed if studies, published in other language than English [74], were excluded. Second, the dichotomization of some data was needed in order to make the ORs of the different studies comparable. Unfortunately, this is inextricably linked to the loss of information. Third, the methodological quality was measured by the adapted NOS for cross-sectional studies, which was also applied for the longitudinal cohort studies, since no other valid alternative was available with the same point spread.

Sleep disturbances are common problems among BCS, but compared with other psychological (e.g., depression, anxiety, etc.) and psychophysiological (e.g., pain, hot flashes, etc.) side effects, they get little attention from clinicians or researchers. A potential explanation for this neglect is that sleep disturbances are frequently seen as a normal and temporary side effect of the diagnosis and/or treatment of breast cancer. Additionally, sleep disturbances are also considered secondary symptom of depression and anxiety disorders, and clinicians rather tend to treat those disorders than the sleep disturbances. Furthermore, the corresponding lack of knowledge in oncologic physicians may lead to underdiagnosis and inadequate care, since the consequences of the sleep disturbances are more often relativized to those of breast cancer by physician and the patients themselves. Therefore, it is important to conduct more and qualitative research about sleep disturbances in BCS [53].

Conclusion

Prevalence numbers for sleep disturbances ranged from 0.14 to 0.93. However, no pooled estimate could be provided given the high heterogeneity among studies, which can be explained be the lack of the proper implementation of the International Classification of Sleep Disorders, appropriate measurement tools, and longitudinal studies. Pain, depressive symptoms, hot flashes, fatigue, non-Caucasian race, and menopausal status were significantly associated with higher odds for development of sleep disturbances, with depressive symptoms being the biggest risk factor.

Despite the fact that this review aimed to provide a comprehensive picture regarding the prevalence and possible risk factors for the development of sleep disturbances in BCS, research up to now can only provide us data on insomnia and sleep-wake disturbances. Other sleep disturbances are missing and require further investigation to come to solid conclusions.

Compliance with ethical standards

Conflict of interest The authors have full control of all data acquired from included manuscripts and agree to allow the journal to review the data if requested.

Appendix 1

Table 4 Search terms

	P		E		O	
	(Breast) cancer survivors		Sleep disturbances		Determinants and prevalence rates	
MeSH terms	Neoplasm Survivors		Sleep-wake disorders Sleep deprivation Sleep Disease		Morbidity Epidemiology Probability Prognosis Epidemiologic factors Etiology Causality Survival analysis Risk	
Free terms	Cancer survivor* Neoplasm* survivor* Post-cancer Cured cancer Cancer survival Malignancy Malignancies Survivorship healed Sarcoma	Cured Post Survivor* Tumor* Tumor* Cancer* Neoplasm Neoplasia* Post-cancer	Sleep disorder* Sleep deprivation* Sleep disturbance* Sleep dysfunction* Sleep syndrome* Pavor nocturnus Sleep wake disorder* Sleep fragmentation* Insufficient sleep Wake disorder* Sleeping sickness	syndrome* Short sleep Insomnia* Parasomnia* Dyssomnia* Night terror Sleeplessness Sleep problem* Sleep disease*	Risk* Etiology Causality Prognosis Cause* Variable* Indicator* Morbidity Incidence Frequenc* Frequency Prognoses Causation* Causalities Outcome* Factor* Predictor* Prediction* Probability Prevalence* Odds ratio* Risk factor*	Relative risk* Hazard ratio* Epidemiology Epidemiologic factor* Survival analysis Determinant* Contributing Characteristic* Prognosticator* Basic reproduction number* Relative frequency Relative incidence Phenomenon Reproduction rate* Reproductive ratio* Prognostic determinant* Prognostic factor* Predisposing factor* Enabling factor* Reinforcing factor* Epidemiologic determinant*

E, exposure; *MeSH*, medical subheading; *O*, outcome; *P*, patient

Appendix 2

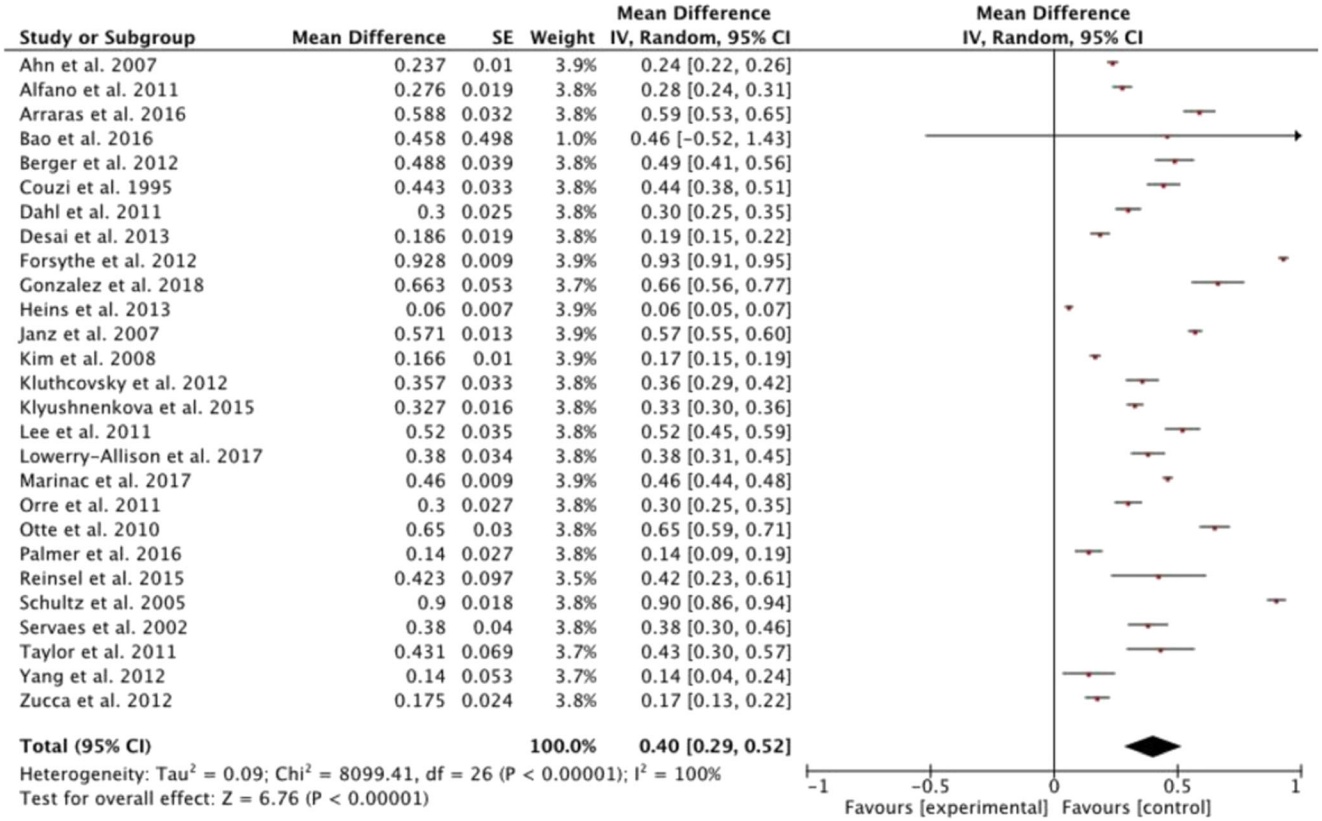

Fig. 3 Prevalence of sleep disturbances in breast cancer survivors

Appendix 3: Methodological quality

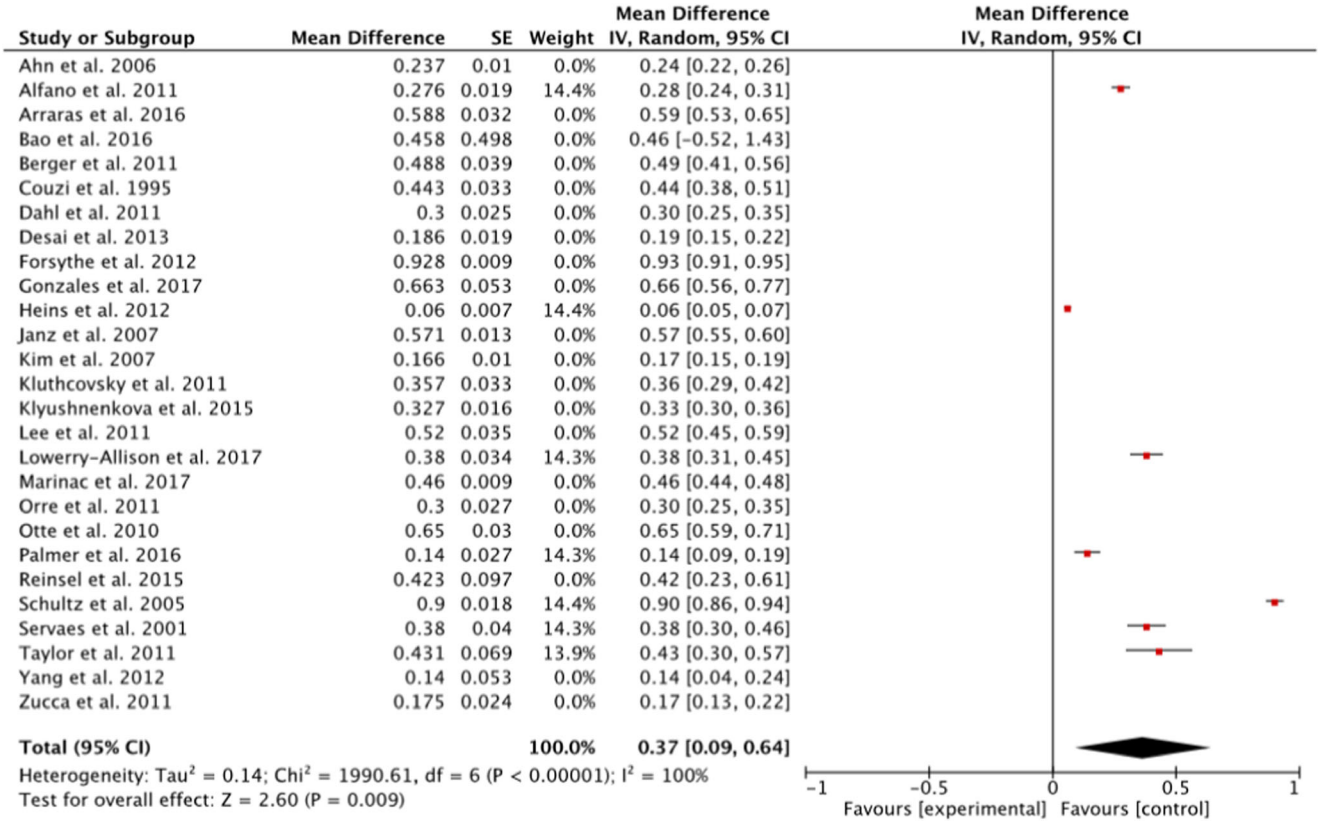

Fig. 4 NOS < 7

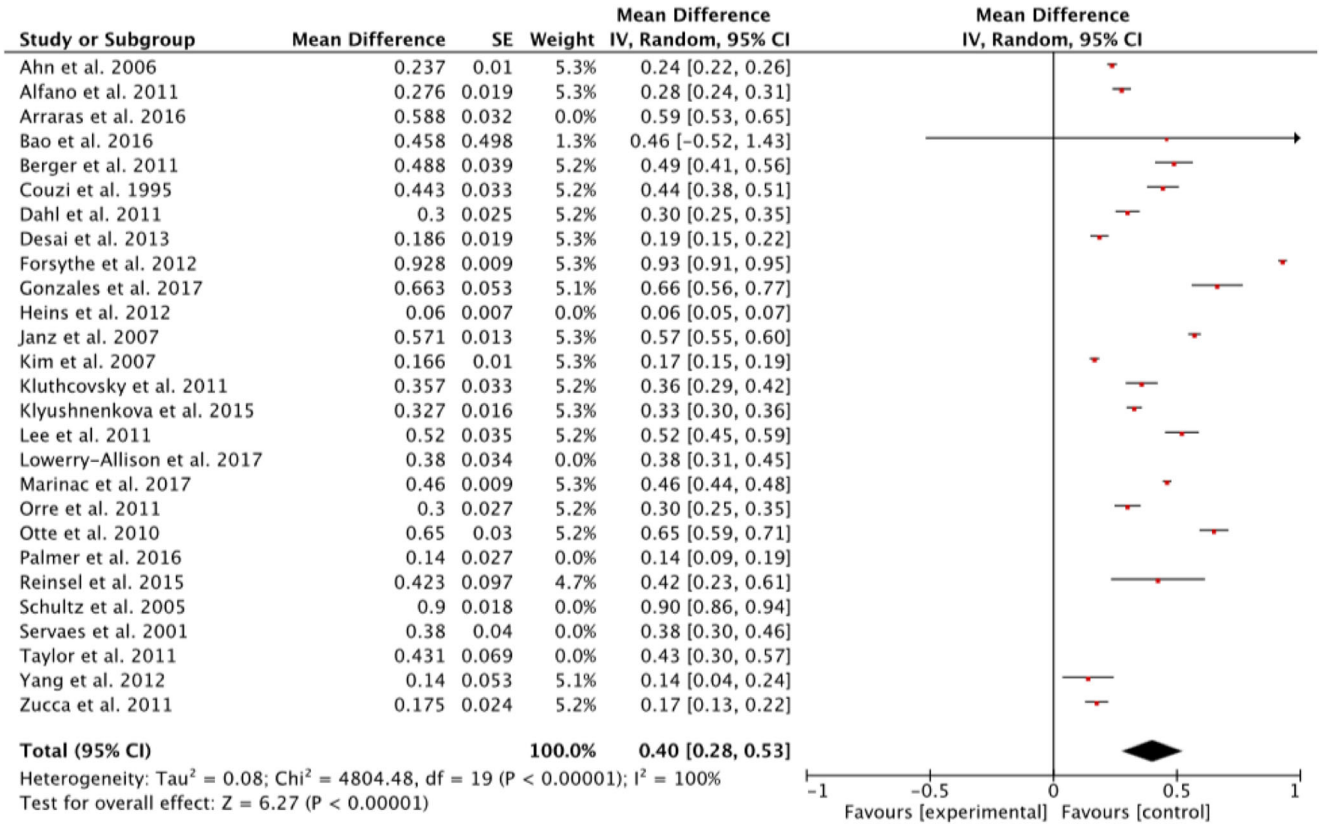
Study or Subgroup
Mean Difference
SE
Weight
Mean Difference IV, Random, 95% CI
Mean Difference IV, Random, 95% CI
Ahn et al. 2006 0.237 0.01 5.3% 0.24 [0.22, 0.26]
Alfano et al. 2011 0.276 0.019 5.3% 0.28 [0.24, 0.31]
Arraras et al. 2016 0.588 0.032 0.0% 0.59 [0.53, 0.65]
Bao et al. 2016 0.458 0.498 1.3% 0.46 [−0.52, 1.43]
Berger et al. 2011 0.488 0.039 5.2% 0.49 [0.41, 0.56]
Couzi et al. 1995 0.443 0.033 5.2% 0.44 [0.38, 0.51]
Dahl et al. 2011 0.3 0.025 5.2% 0.30 [0.25, 0.35]
Desai et al. 2013 0.186 0.019 5.3% 0.19 [0.15, 0.22]
Forsythe et al. 2012 0.928 0.009 5.3% 0.93 [0.91, 0.95]
Gonzales et al. 2017 0.663 0.053 5.1% 0.66 [0.56, 0.77]
Heins et al. 2012 0.06 0.007 0.0% 0.06 [0.05, 0.07]
Janz et al. 2007 0.571 0.013 5.3% 0.57 [0.55, 0.60]
Kim et al. 2007 0.166 0.01 5.3% 0.17 [0.15, 0.19]
Kluthcovsky et al. 2011 0.357 0.033 5.2% 0.36 [0.29, 0.42]
Klyushnenkova et al. 2015 0.327 0.016 5.3% 0.33 [0.30, 0.36]
Lee et al. 2011 0.52 0.035 5.2% 0.52 [0.45, 0.59]
Lowerry-Allison et al. 2017 0.38 0.034 0.0% 0.38 [0.31, 0.45]
Marinac et al. 2017 0.46 0.009 5.3% 0.46 [0.44, 0.48]
Orre et al. 2011 0.3 0.027 5.2% 0.30 [0.25, 0.35]
Otte et al. 2010 0.65 0.03 5.2% 0.65 [0.59, 0.71]
Palmer et al. 2016 0.14 0.027 0.0% 0.14 [0.09, 0.19]
Reinsel et al. 2015 0.423 0.097 4.7% 0.42 [0.23, 0.61]
Schultz et al. 2005 0.9 0.018 0.0% 0.90 [0.86, 0.94]
Servaes et al. 2001 0.38 0.04 0.0% 0.38 [0.30, 0.46]
Taylor et al. 2011 0.431 0.069 0.0% 0.43 [0.30, 0.57]
Yang et al. 2012 0.14 0.053 5.1% 0.14 [0.04, 0.24]
Zucca et al. 2011 0.175 0.024 5.2% 0.17 [0.13, 0.22]
Total (95% CI) 100.0% 0.40 [0.28, 0.53]
Heterogeneity: Tau² = 0.08; Chi² = 4804.48, df = 19 (P < 0.00001); I² = 100%
Test for overall effect: Z = 6.27 (P < 0.00001)
−1
−0.5
0
0.5
1
Favours [experimental]
Favours [control]

Fig. 5 NOS ≥ 7

Appendix 4: Study design

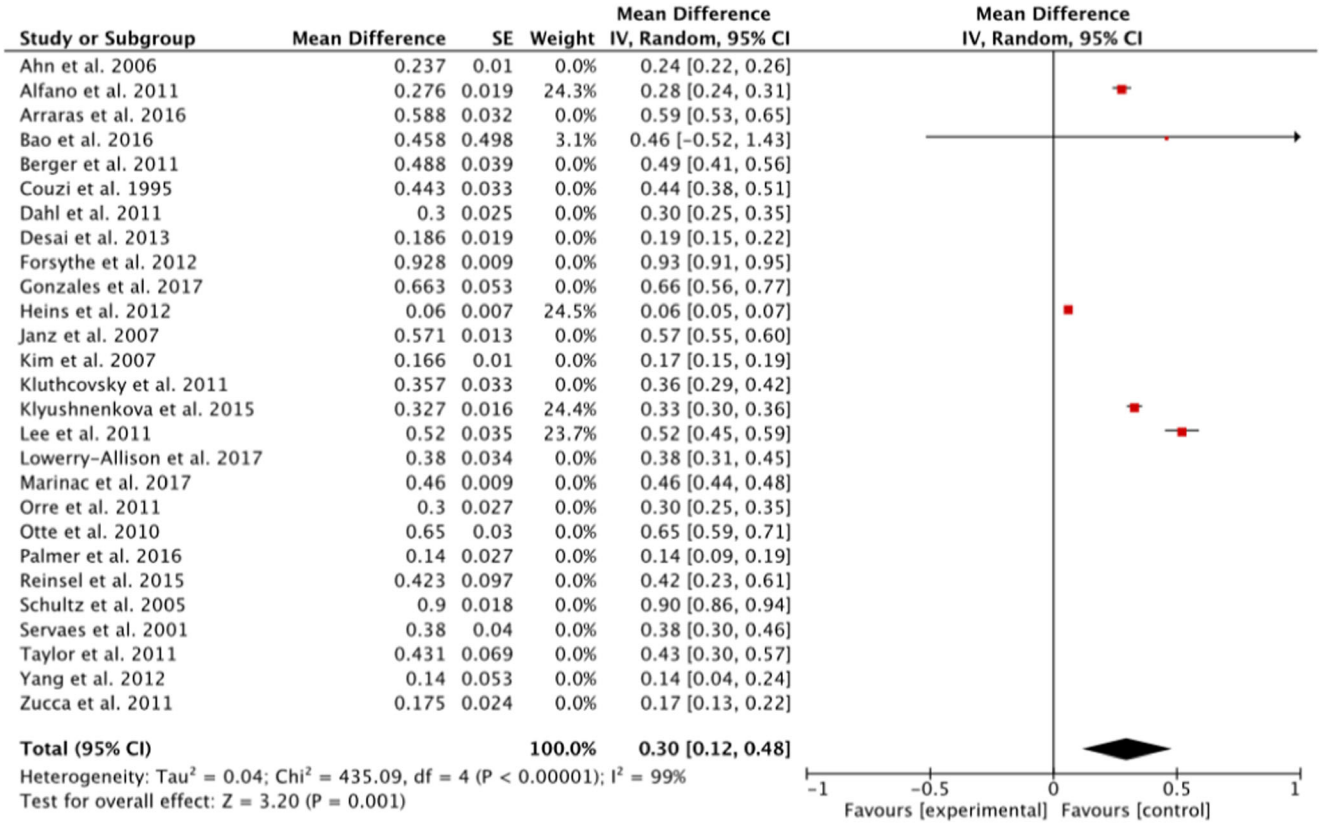

Fig. 6 Longitudinal studies

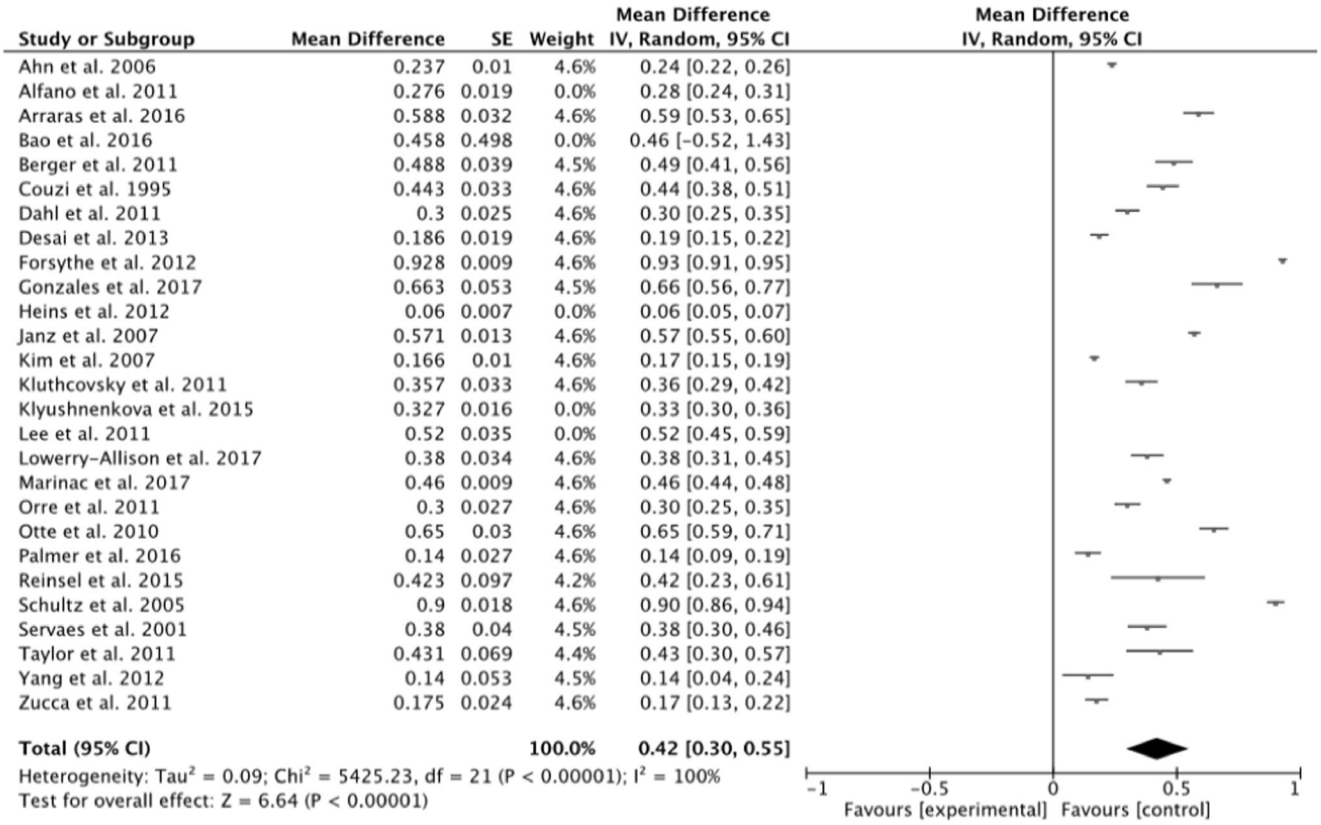

Fig. 7 Cross-sectional studies

Appendix 5: Type of sleep disturbance

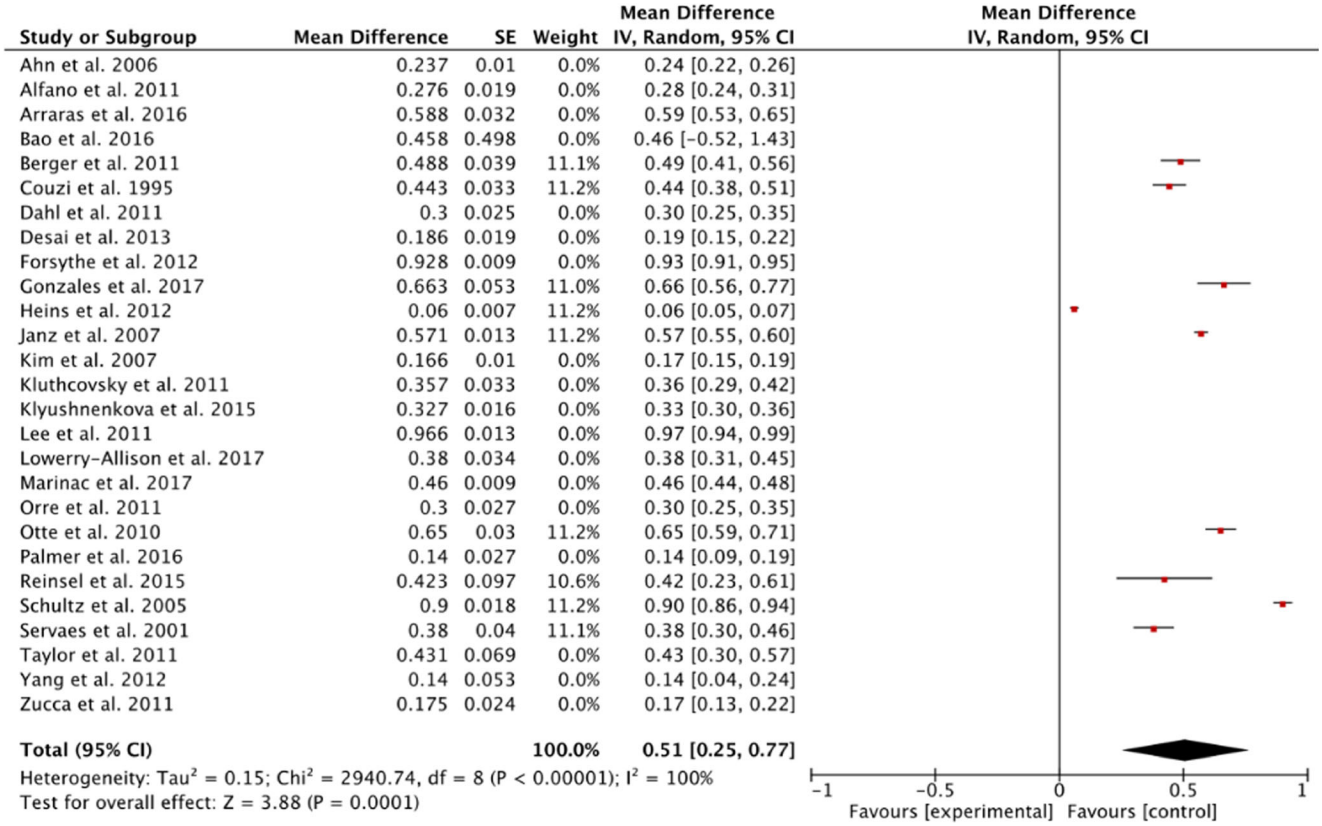

Fig. 8 Sleep-wake disturbance + sleep difficulty

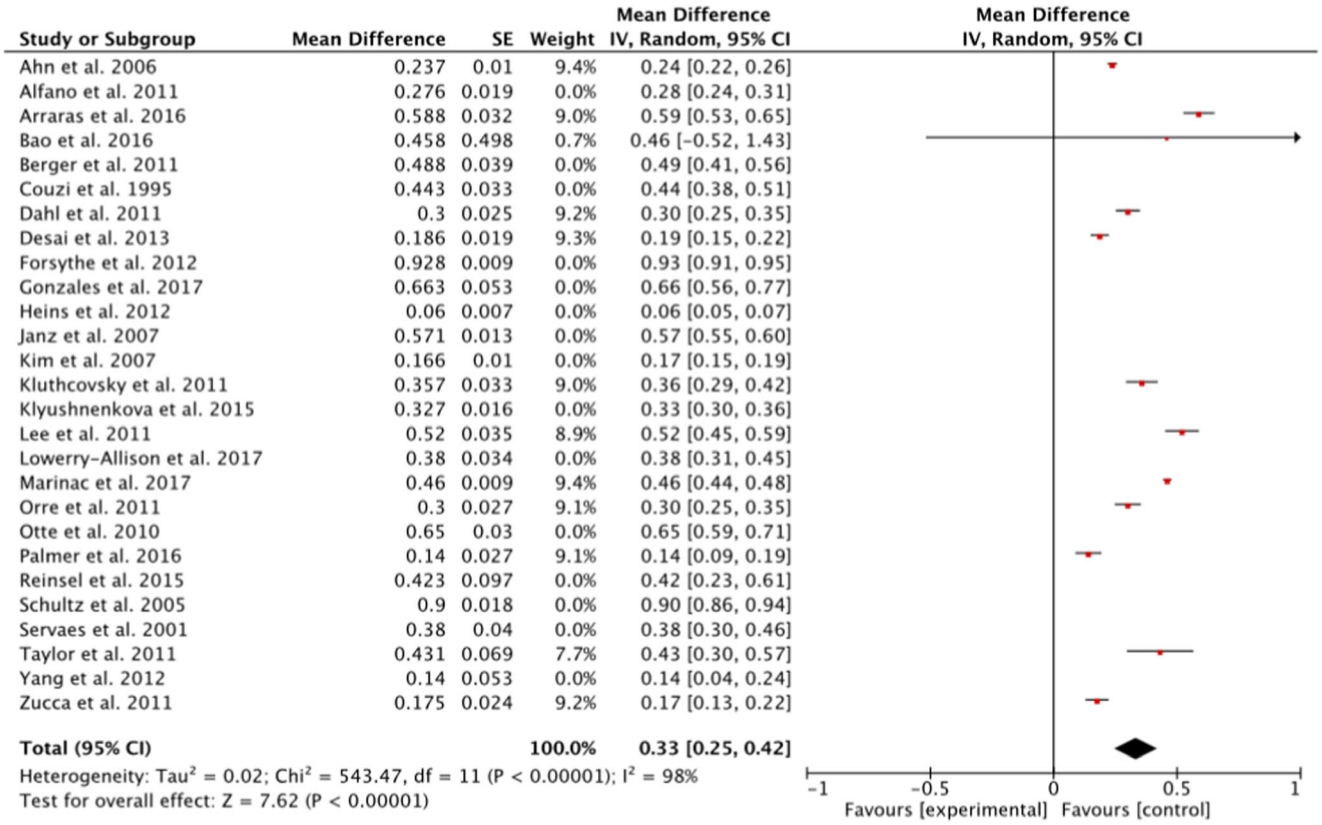

Fig. 9 Insomnia

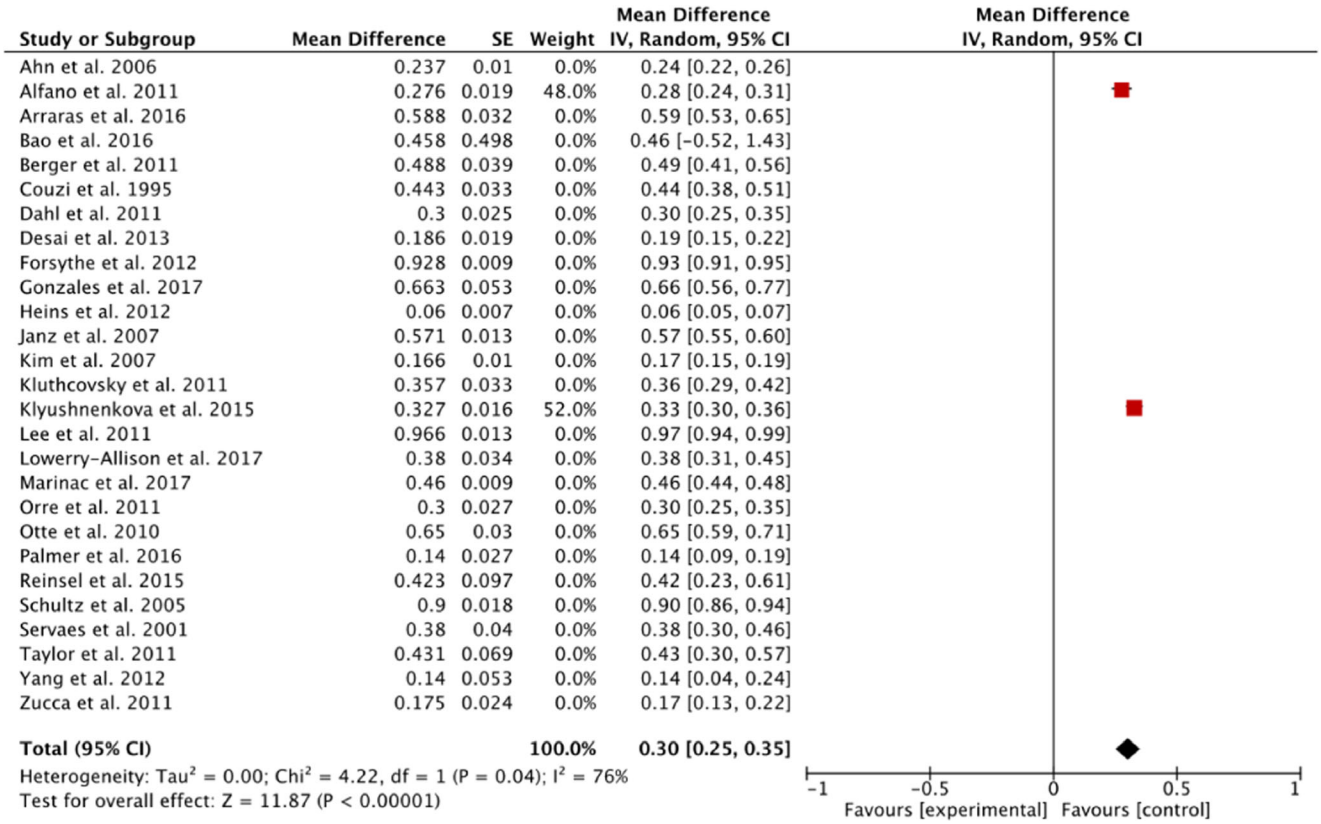

Fig. 10 Short sleepers

Appendix 6

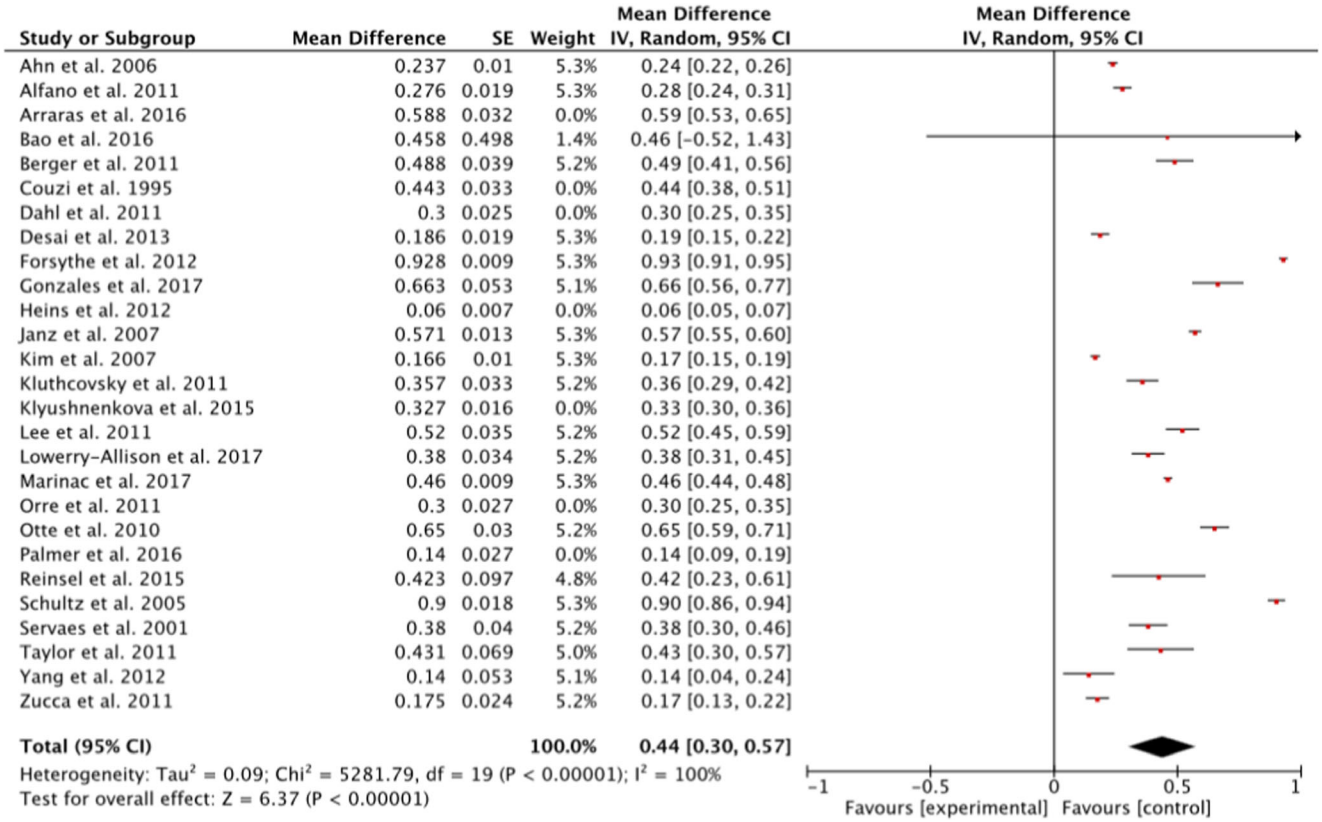

Fig. 11 Validated measurement tool

Appendix 7: Pain

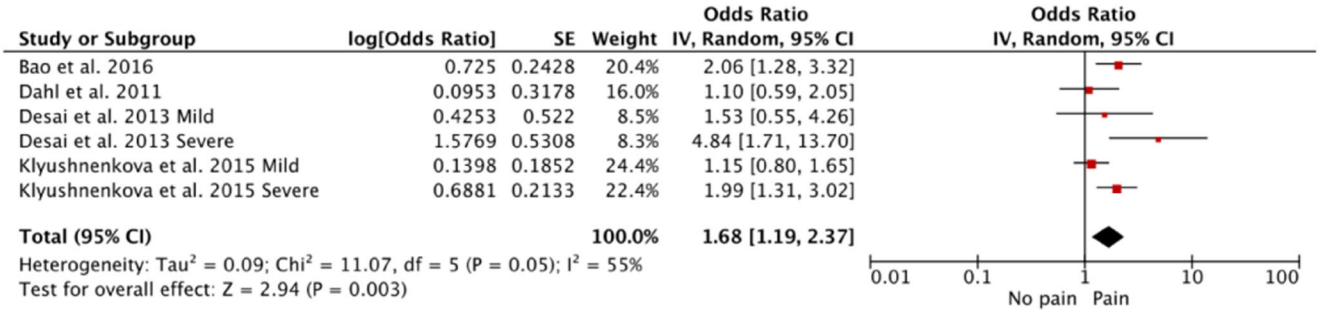

Fig. 12 Pain before subgroup analysis

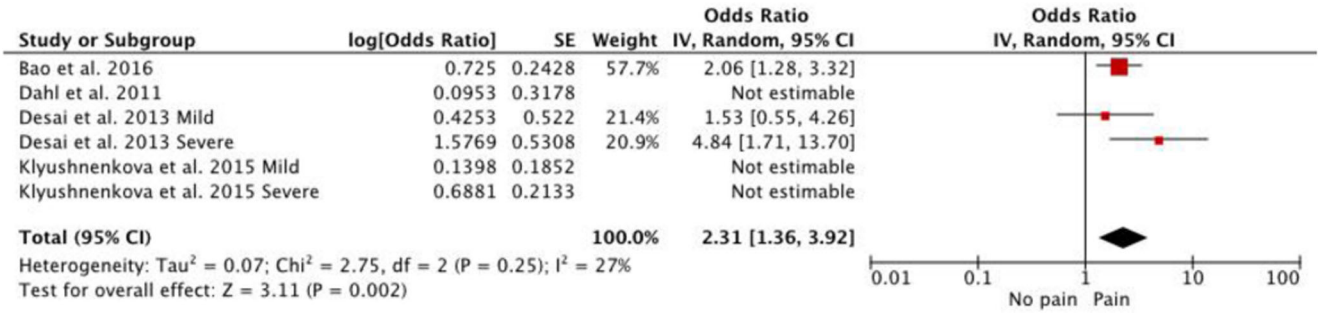

Fig. 13 Pain after subgroup analysis

Appendix 8: Depressive symptoms

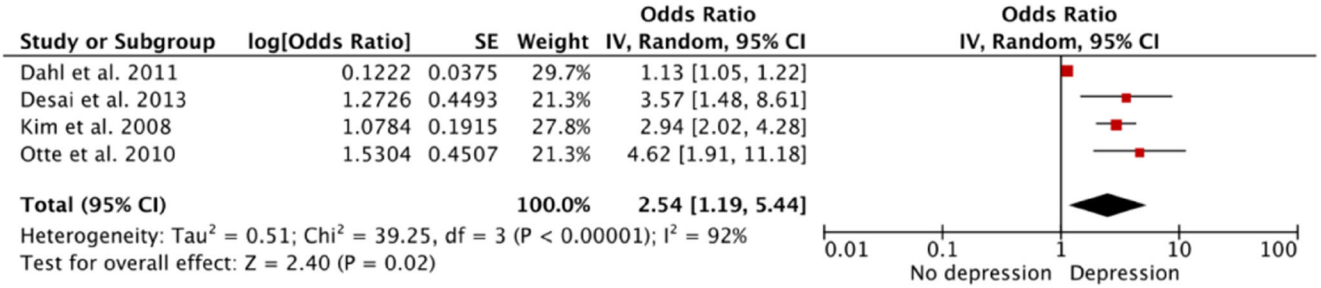

Fig. 14 Depressive symptoms before subgroup analysis

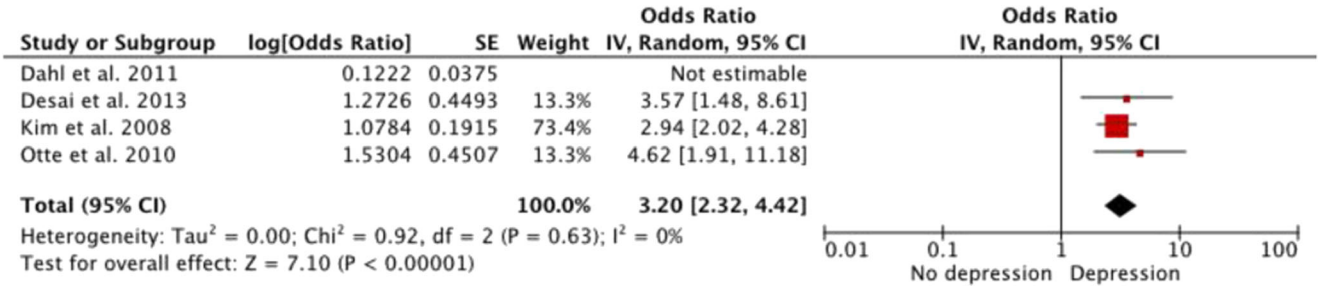

Fig. 15 Depressive symptoms after subgroup analysis

Appendix 9

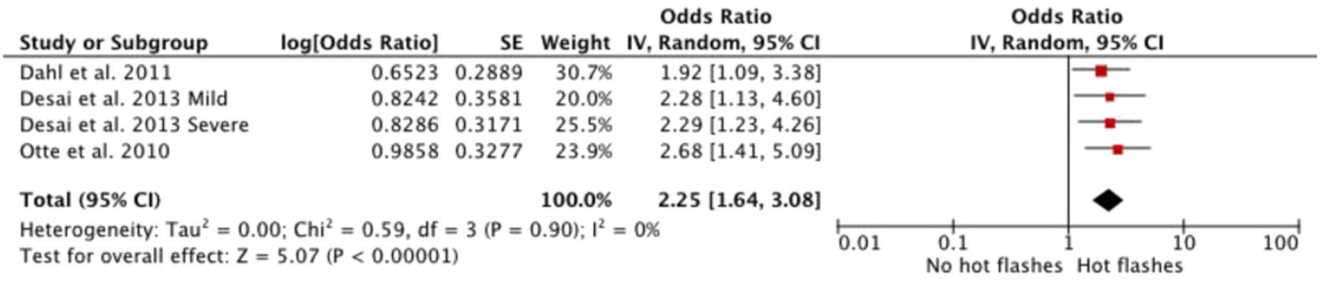

Fig. 16 Hot flashes

Appendix 10: Fatigue

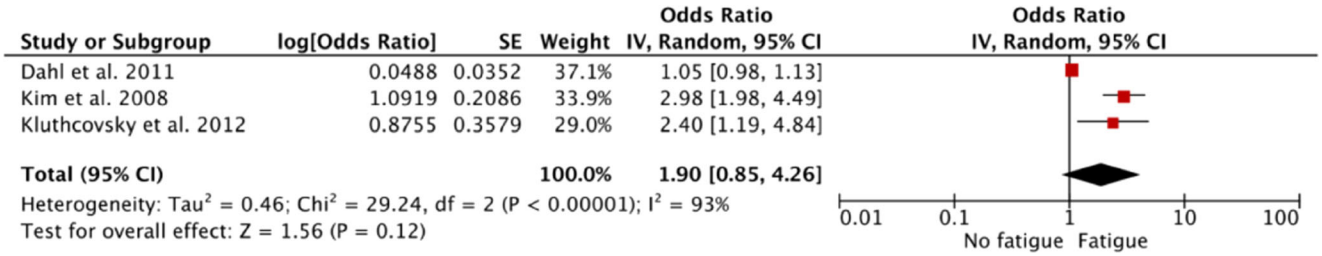

Fig. 17 Fatigue before subgroup analysis

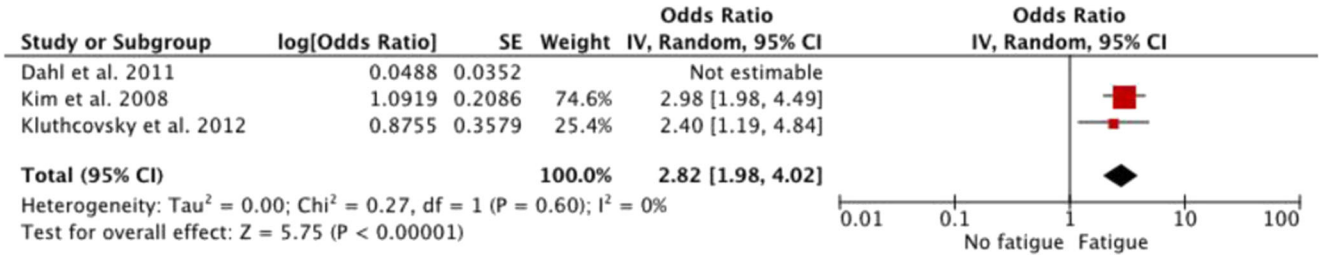

Fig. 18 Fatigue after subgroup analysis

Appendix 11

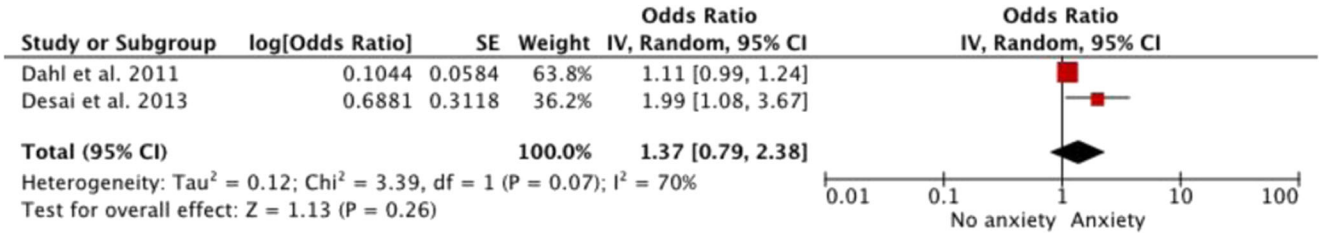

Fig. 19 Anxiety

Appendix 12

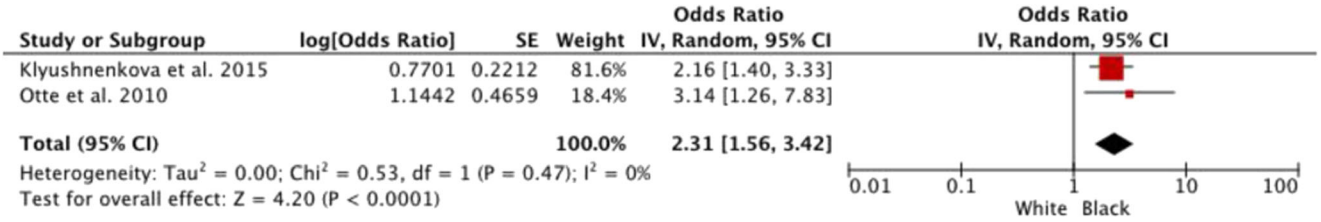

Fig. 20 Race

Appendix 13

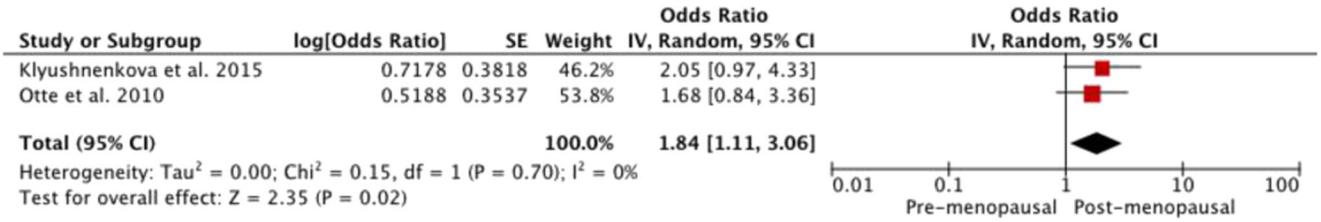

Fig. 21 Menopause

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