

REVIEW ARTICLE

Systematic review and meta-analysis of sleep quality in inactive inflammatory bowel disease

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Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated disorder that involves a complex interplay of genetic and environmental factors.¹ Epidemiological studies have shown increasing incidence of IBD over the past several decades² with strong associations with environmental factors.³ The etiology and exacerbating factors are largely unknown; however, there are known associations with active smoking, urban living, appendectomy, and low vitamin D levels. IBD can be associated with debilitating extraintestinal manifestations including joint, eye, and skin manifestations.⁴ Sleep is likely to be deleteriously affected by the symptoms of active IBD but has also been examined as a

Abstract

Poor sleep in people with inflammatory bowel disease (IBD) has been demonstrated to be prevalent and has been associated with disease activity. This meta-analysis aimed to assess the prevalence of poor sleep in inactive IBD and in controls by considering cohort and cross-sectional studies. Electronic databases were searched for publications from inception to 1 November 2021. Poor sleep and IBD activity were defined according to self-reported subjective sleep measures. A random effects model was used to determine the standardized mean difference between poor sleep in inactive IBD and healthy controls. Publication bias was assessed by funnel plot and Egger's test. Five hundred and nineteen studies were screened with 9 studies included in the meta-analysis incorporating a total of 729 people with IBD and 508 controls. A random effects model showed a standardized mean difference with poor sleep being more frequent in those with inactive IBD than controls with moderate effect size (Hedge's *g* 0.41, CI [0.22–0.59]) and no significant heterogeneity. There was no publication bias evident. Poor sleep is more common in individuals with inactive IBD than healthy controls. Further studies should consider potential mechanisms to explain this result, including the role of subclinical inflammation and psychosocial factors that may influence sleep quality in people with IBD.

potential extraintestinal manifestation of IBD, and as an exacerbating or etiological factor in IBD.

There has been increasing interest in the relationship between sleep and IBD in recent times.⁵ Firstly, sleep has a major role in as an important patient-reported outcome with its relationship to quality of life and health-related outcomes such as cardiovascular disease.⁶ Secondly, impaired sleep quality has been shown to be associated with IBD activity⁷ with worse sleep quality in those with active rather than inactive IBD. One may see this as being related to IBD symptoms and in particular nocturnal symptoms; however, sleep disturbance may also be an indicator of subclinical inflammation, with studies suggesting that endoscopic activity and histological activity in the setting of

clinical remission had high rates of poor sleep.^{8,9} Sleep quality in IBD has also been associated with psychosocial factors such as depression^{10–17} and reduced physical activity.^{18,19}

Two meta-analyses have explored the relationship between IBD activity and sleep quality, with poor sleep being more common in those with IBD compared with controls, and more common in those with active IBD than inactive IBD.^{7,20} These results could be attributed to the symptoms associated with active IBD. The cause of poor sleep in a clinically inactive IBD population is less clear and may relate to subclinical inflammation or mental health co-morbidities among other possibilities. The previous meta-analyses have not considered the difference between sleep quality in clinically inactive IBD and controls.

In this study, we aimed to extend their work by considering the relationship between sleep in clinically inactive IBD and controls and would aim to show that poor sleep is more frequent in those with clinically inactive IBD. Establishing this would support the introduction of sleep quality as an important patient-reported outcome that exists beyond achieving clinical remission. It would also encourage improving sleep quality through known traditional sleep-targeted interventions and investigations rather than focusing only on achieving clinical remission. If we accept that poor sleep in clinically inactive IBD may be due in part to subclinical inflammation, then it may be possible to use sleep quality as a way to monitor IBD and further reinforces the principle of achieving endoscopic rather than symptomatic remission.²¹

Methods

This systematic review and meta-analysis were performed according to the preferred reporting item for systematic reviews and meta-analyses (PRISMA) guidelines.

Search strategy. PubMed, MEDLINE, and PsycINFO were searched from inception to November 2021, including articles published in the English language using the following search string: (sleep OR circadian OR insomnia OR apnoea) AND ([inflammatory bowel disease] OR [Crohn's disease] OR [ulcerative colitis] OR [IBD OR Crohn's OR colitis]).

Eligibility criteria. Studies were included if they met the following criteria: (i) Cross-sectional, observational, case control, cohort, or randomized controlled trial available; (ii) included a distinct population of people with IBD (age ≥ 18 years old) with a definition of inactive disease by subjective measures such as Crohn's disease activity index²² (CDAI), or Harvey-Bradshaw index²³ (HBI), or the partial Mayo score (PMS), or objective measures such as endoscopy; (iii) included a control population of suitably matched controls; and (iv) Sleep quality assessment using a validated subjective patient-reported measures of sleep questionnaire. Unfortunately, there were insufficient number of studies incorporating objective measures of sleep quality or objective measures of IBD activity.

Exclusion criteria included: (i) Study population that included a pediatric or adolescent population; (ii) case report or review.

Study selection. The first author (AB) performed the literature review and two other authors (PS and JB) independently

screened full texts against eligibility criteria, with disagreement resolved by discussion with involvement of another author (RM) when required.

Data collection. Data collection was performed by AB. A predefined spreadsheet was used for data collection.

Study quality assessment. Risk of bias in individual studies was assessed according to study design. Cross-sectional or observational studies were assessed according to modified Newcastle–Ottawa scale. Cohort or case control studies were assessed according to Newcastle–Ottawa scale.

Statistical analysis. Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). Heterogeneity among studies was assessed using the I^2 statistic with $I^2 > 50\%$ considered to indicate substantial heterogeneity. A random effects model was used. A forest plot was performed to estimate individual and pooled effect sizes with associated 95% CI. Hedge's g was used to describe effect size with a Hedge's g of 0.20, 0.50, and 0.80 to interpret effect sizes as small, medium, or large.²⁴ Publication bias was assessed using funnel plots with significant visual asymmetry used to indicate publication bias. The Trimfill method was used as required. Egger's test with P values less than 0.05 were considered to indicate significant publication bias. Subgroup analysis was performed to investigate heterogeneity.

Results

Twenty-one studies were initially identified for inclusion. Nine studies were included in the meta-analysis incorporating 729 people with IBD and 508 controls (see Fig. 1, and Table 1). Publication date ranged from 2006 to 2020. Study quality scoring can be seen in Table S1, Supporting information. IBD study population size ranged from 16 to 110, with median age ranging from 32 to 44 years, and female predominance from 38 to 70%.

IBD disease activity was defined by clinical remission utilizing subjective IBD activity scores such as the CDAI, with similar cutoff values used across studies to define remission. A single study used physician assessment of disease activity and one study required stable therapy for 6 months in addition to physician assessment. Sleep quality was assessed using the Pittsburgh Sleep Quality index²⁵ (PSQI) in all studies. The PSQI produces a global sleep score along with six sub-scores to assess sleep latency, sleep duration, sleep disturbance, subjective sleep quality, sleep medications, and daytime sleepiness. All studies used the same definition of poor sleep quality (PSQI global score > 5). Studies were designed to consider other factors that may influence sleep quality alongside IBD activity. This includes psychological distress,¹⁵ mood disturbance¹⁰ or depression,²⁶ and the presence of extra-articular manifestations.

Control groups consisted of relatives or friends of study participants, gastrointestinal clinic patients with normal endoscopic investigations, or volunteers identified via online or university recruitment without gastrointestinal disease. All studies required controls having no gastrointestinal disease with some requiring no autoimmune disease. Age matching was performed

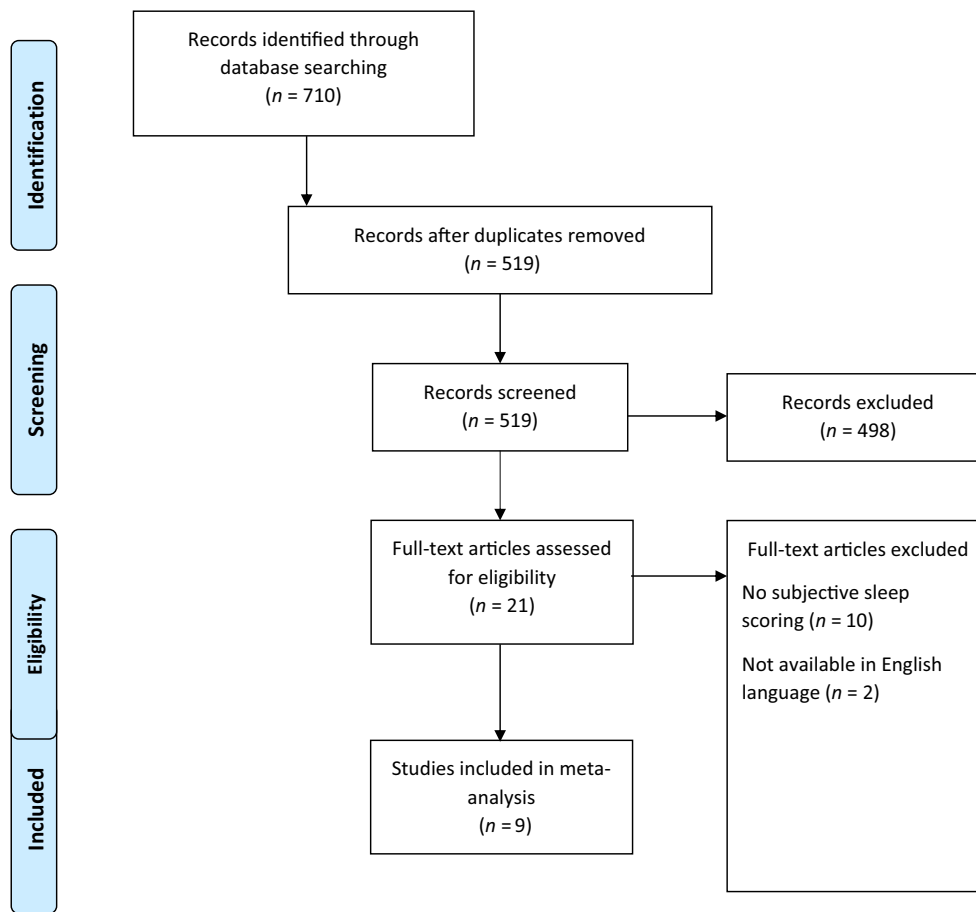


Figure 1 PRISMA flowchart—Selection of studies and results of literature search for review and meta-analysis.

in one study,²⁷ and one study utilized age, sex, and body mass index matching.¹⁰ No other matching was undertaken.

Ballou *et al.*²⁸ assessed subjective sleep quality in a population of gastroenterology clinic patients that included people with IBD in clinical remission with sleep quality worse than controls, however did find that people with irritable bowel syndrome had worse sleep than those with IBD. Bucci *et al.*²⁹ similarly found worse sleep in those with clinically inactive IBD than controls while investigating the prevalence and associations of bruxism in this population. However, Gingold-Belfer *et al.*,³⁰ considering only those with Crohn's disease, found that IBD activity was associated with poor sleep but observed no difference in those with inactive Crohn's disease and controls.

Gilc-Blanariu *et al.*¹⁵ considered other factors that may influence sleep in people with IBD and found that psychological distress and extraintestinal manifestations were associated with poor sleep. Sochal *et al.*¹⁰ similarly investigated factors influencing sleep quality in IBD and found that mood levels were related to sleep quality and interestingly that pain scores were not related. This perhaps somewhat explains the poor sleep experienced by people with clinically inactive IBD.

Iskandar *et al.*²⁶ used wrist-based actigraphy to provide an objective measurement of sleep quality, finding no difference

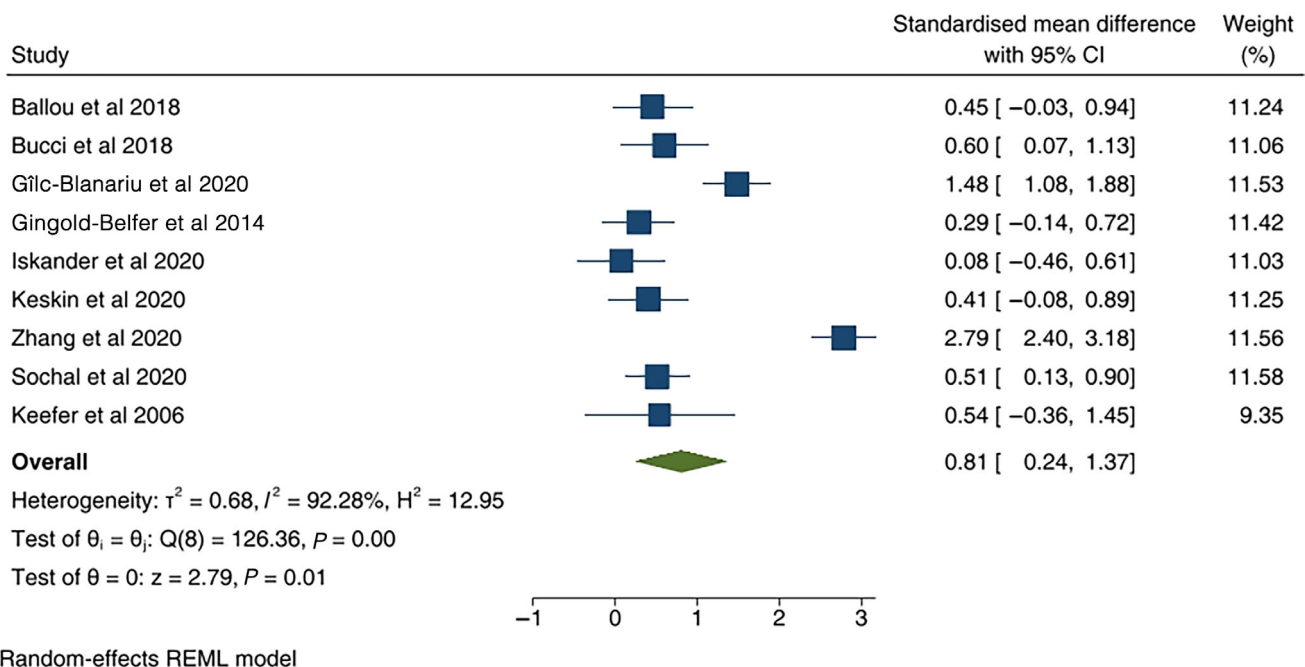
between people with Crohn's disease and controls, suggesting that it was only the perception of sleep quality that was worse in Crohn's disease than controls. Zhang *et al.*³¹ using polysomnography to measure objective sleep quality found significantly worse sleep in those with IBD and controls irrespective of IBD activity. The differences here in the study outcome can be explained by the short comings of actigraphy in assessing sleep quality compared with polysomnography,³² which is considered the gold standard of assessing sleep. One further study,³³ also using polysomnography, was able to show worse objective sleep quality in those with IBD than controls despite a small study size. Due to the small number of studies ($n = 3$) incorporating objective sleep quality further analysis was not undertaken.

A meta-analysis was performed incorporating nine studies that utilized subjective measures of sleep quality and subjective measures of IBD activity. Effect sizes were calculated using the standardized mean difference calculated (pooled Hedge's g of 0.81 CI [0.24–1.37]), indicating moderate effect size of increased likelihood of poor sleep in those with inactive IBD compared with controls (see forest plot in Fig. 2). Heterogeneity was significant with I^2 92.3%. Outliers were removed^{15,31} with moderate effect size again shown (Hedge's g 0.41, CI [0.22–0.59]), and with no significant heterogeneity (I^2 0%) (see forest plot in Fig. S1, Supporting

Table 1 Summary of studies included in meta-analysis of sleep quality in inflammatory bowel disease and controls

Study	Year	Country	Sample size	Age (mean)	Female (%)	Definition of inactive IBD	Definition of poor sleep	Type of controls	Study summary
Ballou <i>et al.</i> ²⁸	2018	United States	IBD 44 Controls 41	IBD 44 Controls 42	IBD 70% Controls 56%	HBI ≤4 PMS ≤1	PSQI >5	Friends and family of study participants who do not have gastrointestinal diseases.	Tertiary gastrointestinal center patients have poorer sleep than controls
Bucci <i>et al.</i> ²⁹	2018	Italy	CD 28 UC 19 Controls 47	CD 38 UC 40 Controls 34		Stable therapy for 6 months physician assessment	PSQI >5	Volunteers with no gastroenterological disease, no infectious, immune-mediated, or autoimmune diseases	Bruxism and enamel wear should be evaluated in people with Crohn's disease
Gilc-Blaniariu <i>et al.</i> ¹⁵	2020	Romania	IBD 110 Controls 66	IBD 42 Controls 44	IBD 47% Controls 60%	HBI ≤4 PMS ≤1	PSQI >5	Healthy volunteers with no digestive complaints and a normal colonoscopy	Sleep impairment is common in those with IBD and associated with psychological distress
Gingold-Belfer <i>et al.</i> ³⁰	2014	Israel	CD 71 Controls 66	CD 40 Controls 42	CD 38% Controls 54%	CDAI <150	PSQI >5	Healthy volunteers accompanying a relative having a screening colonoscopy	Poor sleep is associated with active Crohn's disease but not inactive disease
Iskander <i>et al.</i> ²⁶	2020	United States	CD 61 Controls 60	CD 32 Controls 31.5		HBI ≤4	PSQI >5	Health volunteers through university program to support research	Crohn's disease report poorer sleep than controls but no difference is seen based on objective measures
Keskin <i>et al.</i> ²⁷	2020	Turkey	CD 41 UC 49 Controls 44	CD 33 UC 40 Controls 40	CD 56 UC 55 Controls 70	Physician assessment	PSQI >5	Age-matched individuals without any chronic disease	IBD is a risk factor for sleep disturbance and eveningness is more common in IBD than controls
Keefer <i>et al.</i> ³³	2006	USA	IBD 120 Controls 120	IBD 36 Controls 36	IBD 49 Controls 45	CDAI <150 UCAI <3	PSQI >5	Healthy volunteers from university gastroenterology practice	Sleep influences quality of life in those with IBD and controls
Sochal <i>et al.</i> ¹⁰	2020	Poland	IBD 133 Controls 57	IBD 37 Controls 38	IBD 55 Controls 58	HBI ≤4 PMS ≤2	PSQI >5	Healthy volunteers via snowball sampling matched by age, sex, and BMI	Sleep impairment is common in IBD and associated with mood disturbance
Zhang <i>et al.</i> ³¹	2020	China	IBD 16 Controls 7	IBD 41 Controls 34	IBD 56% Controls 43%	HBI ≤4 PMS ≤1	PSQI >5	Healthy volunteers from online recruitment	Sleep in people with IBD was worse than the control group, and even worse in the IBD-PA group

CD, Crohn's disease; CDAI, Crohn's disease activity index; HBI, Harvey-Bradshaw index; IBD, inflammatory bowel disease; IBD-PA, inflammatory bowel disease with active peripheral arthropathy; PMS, partial Mayo score; PSQI, Pittsburgh Sleep Quality index; UC, ulcerative colitis; UCDAI, ulcerative colitis disease activity index.



Random-effects REML model

Figure 2 Forest plot of poor sleep in those with clinically inactive inflammatory bowel disease and controls. Standardized mean difference is used as effect size. Outliers included.

information). Funnel plot was symmetric (Fig. S2, Supporting information) and Egger's test was negative ($P = 0.37$).

Subgroup analysis was performed for definition of inactive IBD (HBI ≤ 4 and PMS ≤ 2 , opposed to other definitions, $P = 0.20$) and was not significant, along with gender (female gender in over half of population, $P = 0.15$) and was not significant. Subgroup analysis was also performed for subtype of IBD (Crohn's disease over half of population, $P = 0.14$) and was not significant. There were insufficient studies to investigate further with meta regression.

Discussion

Herein we have shown that clinically inactive IBD patients demonstrate poorer subjective sleep quality than controls. This represents an important result in pursuing the etiology of poor sleep quality in people with IBD. There has been the presumption that nocturnal GI symptoms were the primary driver of poor sleep quality in this population. Although such symptoms are likely to impair sleep quality, inactive IBD may also impact sleep through a variety of mechanisms.

These mechanisms could include subclinically active IBD. Two studies, one utilizing endoscopic⁸ and the other histologic⁹ measures, showed that subclinically active IBD is associated with poor sleep compared with IBD in remission. It may be that there are specific sleep abnormalities that are associated with subclinically active IBD. There were insufficient studies incorporating objective measures of IBD activity or objective measures of sleep to pursue this further.

There is a complex relationship between the immune system and sleep, which leads to the possibility that IBD-related inflammation may lead to poor sleep irrespective of the

symptoms experienced. Sleep deprivation has been shown to lead to a rise in pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF α ³⁴ that have also been implicated in the pathogenesis of IBD. Furthermore, abnormalities in circadian rhythm associated clock genes³⁵ and sleeping duration³⁶ have been associated with the development of IBD and ulcerative colitis, respectively. The relationship between sleep and IBD has consequently been said to be bidirectional, with the prospect of feedback between each leading to deterioration of both.

Irritable bowel syndrome frequently coexists with IBD and has also been associated with poor sleep compared with healthy controls,³⁷ despite there being little evidence of systemic inflammation in IBS. Consideration therefore needs to be given to the possibility that persistent GI symptoms irrespective of disease activity, such as the so-called post-inflammatory syndrome or irritable bowel syndrome, contribute to poor sleep in those with IBD. This is supported by Zargar *et al.*,³⁸ showing that those with IBD in remission who met diagnostic criteria for IBS had poorer sleep than those not meeting criteria.

Other contributors to poor sleep in inactive IBD may include differences in levels of physical activity or age, both known to be associated with poor sleep.³⁹ Mental health conditions such as anxiety and depression are prevalent in IBD and have been demonstrated to influence sleep.^{10–17} It has also been hypothesized that this poor sleep may represent "learned insomnia" from previous active IBD and may respond well to targeted insomnia treatment such as specific cognitive behavioral therapy, with a recent feasibility study showing encouraging results.⁴⁰

Limitations of this analysis include lack of matching, which was performed in two studies only. Other factors known to impact sleep and are known to be prevalent in IBD, such as depression and anxiety, could have been considered for

matching. Geographic origin of study and publication date were diverse. Unfortunately, there were insufficient studies to consider objective measures of sleep quality such as polysomnography or actigraphy. This should be pursued in future work.

Further research is required to investigate whether sleep abnormalities are associated with subclinical disease activity, defined by histological or endoscopic activity, or whether other non-inflammation-related factors such as psychological symptoms account for this impairment of sleep in those with inactive disease.

Sleep assessment may become an important PRO and allow early identification of IBD activity before the onset of clinical symptoms. After further defining key contributors to this problem, further research should focus on sleep-specific interventions in people with IBD and the impact these interventions may have on both disease activity and quality of life and in people living with IBD.

Conclusion

This meta-analysis has shown that poor sleep assessed by subjective measures is more frequent in those with clinically inactive IBD than controls with moderate effect size. This suggests that sleep quality in people with IBD is not only due to IBD-related symptoms and encourages investigation of those with poor sleep quality and consideration of sleep-targeted interventions. Of much interest is the limited data that suggest that subclinical IBD-related inflammation may be responsible for poor sleep.^{8,9} Consequently, poor sleep in the absence of IBD-related symptoms could prompt consideration of objective IBD assessment. Further research should consider what sleep interventions may be most efficacious and well tolerated in an IBD population.

Data availability statement. The data underlying this article are available in the Harvard Dataverse Digital Repository at <https://doi.org/10.7910/DVN/ZNF52C>.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Forest plot of poor sleep in those with clinically inactive inflammatory bowel disease and controls. Standardized mean difference used as effect size. Outliers excluded.

Figure S2. Funnel plot of meta-analysis of poor sleep in those with clinically inactive inflammatory bowel disease and controls. Standardized mean difference used as effect size.

Table S1. Study quality scored according to the Newcastle-Ottawa scale with sub-scores and associated study quality detailed.