



## King's Research Portal

DOI:

[10.1001/jamapsychiatry.2022.4599](https://doi.org/10.1001/jamapsychiatry.2022.4599)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Bagautdinova, J., Mayeli, A. M., D. Wilson, J., Donati, F. L., Colacot, R. M., Meyer, N., Fusar-Poli, P., & Ferrarelli, F. (2023). Sleep abnormalities in different clinical stages of psychosis: A systematic review and meta-analysis. *JAMA Psychiatry*, 80(3), 202-210. <https://doi.org/10.1001/jamapsychiatry.2022.4599>

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

# Sleep abnormalities in different clinical stages of psychosis: A systematic review and meta-analysis

Joëlle Bagautdinova\*<sup>1</sup>, MSc, Ahmad Mayeli<sup>2\*†</sup>, PhD, James D. Wilson<sup>2</sup>, PhD, Francesco L. Donati<sup>2,3</sup>, MD, Rebekah M. Colacot<sup>4</sup>, BS, Nicholas Meyer<sup>5</sup>, MD, PhD, Paolo Fusar-Poli<sup>6,7</sup>, MD, PhD, Fabio Ferrarelli<sup>2†</sup>, MD, PhD

<sup>1</sup>Department of Neuroscience, University of Pennsylvania, USA

<sup>2</sup>Department of Psychiatry, University of Pittsburgh, USA

<sup>3</sup>Department of Health Sciences, University of Milan, Italy

<sup>4</sup>Department of Neuroscience, University of Pittsburgh, USA

<sup>5</sup>Department of Psychosis Studies, Institute of Psychology, Psychiatry and Neuroscience, King's College London  
King's College London, UK

<sup>6</sup>Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom

<sup>7</sup>Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

## \* Co-first authors

Joëlle Bagautdinova and Ahmad Mayeli

## † Corresponding Authors:

Fabio Ferrarelli, MD PhD

3501 Forbes Ave, Suite 456, Pittsburgh, PA 15213

Telephone Number: (412) 864-1668

Email: [ferrarellif@upmc.edu](mailto:ferrarellif@upmc.edu)

Ahmad Mayeli, PhD

3501 Forbes Ave, Suite 715, Pittsburgh, PA 15213

Email: [mayelia@upmc.edu](mailto:mayelia@upmc.edu)

**Date of revision:** 11/07/2022

**Word count:** 3462

## 33 Key points

- 34 • **Question:** Do sleep abnormalities differ in occurrence and severity in clinical high-risk  
35 (CHR-P), early psychosis (EP), and chronic psychosis (CP)?
- 36 • **Findings:** Sleep disturbance prevalence across 5135 cases was 50% and was comparable  
37 across psychosis stages. Comparing 1575 cases and 977 controls revealed poor self-  
38 reported sleep quality throughout stages. CP had more arousal vs. CHR-P and reduced  
39 spindle duration vs. EP.
- 40 • **Meaning:** These findings indicate that a) sleep disturbances are highly prevalent  
41 throughout psychosis stages; b) CHR-P, EP, and CP show common and distinct self-  
42 reported and objective sleep alterations, thus representing clinical targets and research  
43 domains for psychosis.

44

45

46

47

48

49

50

51

52

53

54

55

## 56 Abstract

57 **Importance:** Abnormal sleep is frequent in psychosis; however, sleep abnormalities in different  
58 stages (i.e., Clinical-High-risk for Psychosis (CHR-P), Early Psychosis (EP), and Chronic  
59 Psychosis (CP)) have not been characterized.

60 **Objective:** Identify sleep abnormalities across psychosis stages.

61 **Data sources:** Web of Science and PubMed were searched between inception and June 15<sup>th</sup>,  
62 2022.

63 **Study selection:** Sleep disturbance prevalence studies and case-control studies reporting sleep  
64 quality, sleep architecture, or sleep EEG oscillations in CHR-P, EP, or CP.

65 **Data Extraction and Synthesis:** This meta-analysis (PROSPERO; [CRD42021240503](https://doi.org/10.1111/chrp.12405)) followed  
66 PRISMA 2020 guidelines. Stage-specific and pooled random-effects meta-analyses were  
67 conducted, along with the assessment of heterogeneity, study quality, and meta-regressions  
68 (clinical stage, sex, age, medication status, psychotic symptoms).

69 **Main Outcomes and Measures:** Sleep disturbance prevalence, self-reported sleep quality, sleep  
70 architecture (total sleep time, sleep latency, sleep efficiency, NREM and REM stages, number of  
71 arousals), and sleep EEG oscillations (spindle density, amplitude, and duration, and slow wave  
72 density).

73 **Results:** Fifty-nine studies with up to 6710 cases (N= 5135 for prevalence) and 977 controls  
74 were included. Sleep disturbance prevalence in pooled cases was 50% (95%CI=40-61%) and it  
75 was similar in each psychosis stage. Sleep quality was worse in pooled cases vs. controls  
76 (standardized mean difference, SMD=1.00, 95%CI=[0.70-1.30]). Sleep architecture alterations  
77 included: higher sleep onset latency (pooled cases SMD=0.96[0.62-1.30], EP SMD=0.72[0.52-

78 0.92], CP SMD=1.36[0.66-2.05]), higher wake after sleep onset (pooled cases SMD=0.5[0.29-  
79 0.71], EP SMD=0.62[0.34-0.89], CP SMD=0.51[0.09-0.93]), higher number of arousals (pooled  
80 cases SMD=0.45[0.07-0.83], CP SMD=0.81[0.30-1.32]), higher stage 1 sleep (pooled cases  
81 SMD=0.23[0.06-0.40], EP SMD=0.34[0.15-0.53]), lower sleep efficiency (pooled cases SMD=-  
82 0.75[-0.98 to -0.52], EP SMD=-0.90[-1.20 to -0.60], CP SMD=-0.73[-1.14 to -0.33]), and lower  
83 rapid eye movement density (pooled cases SMD=0.37[0.14-0.60], CP SMD=0.48[0.19-0.77]).  
84 Spindle parameter deficits included density: pooled cases SMD=-1.06[-1.50 to -0.63], EP  
85 SMD=-0.80[-1.22 to -0.39], CP SMD=-1.39[-2.05 to -0.74]; amplitude: pooled cases SMD=-  
86 1.08[-1.33 to -0.82], EP SMD=-0.86[-1.24 to -0.47], CP SMD=-1.25[-1.58 to -0.91]; and  
87 duration: pooled cases SMD=-1.21[-1.69 to -0.73], EP SMD=-0.71[-1.08 to -0.34], CP SMD=-  
88 1.74[-2.10 to -1.38]. Furthermore, CP had more frequent arousals vs. CHR-P ( $z=2.24$ ,  $p=0.02$ ),  
89 and reduced spindle duration vs EP ( $z=-3.91$ ,  $p<0.001$ ).

90 **Conclusion:** Sleep disturbances are highly prevalent throughout the course of psychosis, and  
91 different psychosis stages show both shared and distinct abnormalities in sleep quality,  
92 architecture, and spindles. Thus, sleep should become a core clinical target and research domain  
93 from at-risk to early and chronic stages of psychosis.

94

95

96

97

98

99

100

101

## 102 Introduction

103 Sleep abnormalities have been observed in psychotic disorders since the dawn of psychiatric  
104 literature<sup>1</sup>. Sleep disturbances, such as insomnia, are commonly reported by individuals with  
105 chronic psychosis (CP)<sup>2</sup> and are associated with subsequent relapse<sup>3</sup>. Altered sleep often  
106 precedes a psychotic episode in early psychosis (EP)<sup>4</sup>, and disrupted sleep contributes to  
107 predicting transition to psychosis in youth at clinical high risk (CHR-P)<sup>5</sup>. Thus, sleep  
108 abnormalities not only co-occur with psychotic symptoms but are also implicated in the  
109 development, manifestation, and recurrence of psychosis<sup>6</sup>.

110 Sleep disturbance prevalence, which is usually assessed with self-reported questionnaires (e.g.,  
111 the Pittsburgh Sleep Quality Index, PSQI)<sup>7</sup> is ~25% in the general population<sup>7,8</sup>. Several studies  
112 have reported higher sleep disturbance prevalence in psychosis, although rates vary substantially  
113 (21-100%)<sup>9-11</sup> and have thus far never been meta-analyzed in different psychosis stages.

114 Altered sleep patterns across psychosis stages can also be examined in case control comparisons.  
115 Several case control studies have used subjective sleep assessments (e.g., PSQI), which are  
116 inexpensive and easy to implement in large clinical cohorts, and have reported worse sleep  
117 quality in CHR-P<sup>12</sup>, EP<sup>13</sup>, and CP<sup>14</sup> vs. healthy comparison groups. Other sleep studies have  
118 utilized actigraphy, electroencephalography (EEG), and polysomnography (PSG) to objectively  
119 quantify altered sleep characteristics in psychosis. Traditionally, these studies have focused on  
120 sleep architecture. Meta-analyses of sleep architecture findings from actigraphy<sup>15</sup> and PSG/EEG  
121 studies<sup>16-18</sup> revealed shorter total sleep time and longer sleep onset latency and wake after sleep

122 onset in CP. PSG/EEG studies also showed decreased deep NREM sleep and reduced latency  
123 and duration of REM sleep in these patients<sup>18</sup>. Furthermore, shorter total sleep time and larger  
124 wake after sleep onset were reported in EP and CHR-P<sup>19</sup>, suggesting that altered sleep  
125 architecture is an early feature of psychosis.

126 More recently, several studies investigated sleep-specific EEG oscillations, including spindles, in  
127 psychosis. Deficits in spindle parameters (i.e., density, amplitude, and duration) were established  
128 in CP<sup>20</sup> and EP<sup>21,22</sup>. Furthermore, a recent meta-analysis reported reduced spindle density in  
129 psychotic disorders that yielded large effect sizes and was associated with disease progression<sup>23</sup>.

130 Systematically investigating the occurrence and severity of sleep abnormalities in CHR-P, EP,  
131 and CP may therefore help differentiate sleep dysfunctions associated with chronicity and long-  
132 term medication exposure (i.e., observed only/primarily in CP) from those implicated in the  
133 manifestation of full-blown psychosis (i.e., occurring first in EP) and from sleep alterations  
134 related to vulnerability to psychosis (i.e., present since CHR-P)<sup>24</sup>. This meta-analysis assessed,  
135 for the first time, the prevalence of sleep disturbances, along with subjective and objective sleep  
136 alterations throughout the course of psychosis, including CHR-P, EP, and CP.

## 137 Methods

138 This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-  
139 analyses (PRISMA) 2020<sup>25</sup> guidelines. The protocol was registered in PROSPERO  
140 ([CRD42021240503](https://doi.org/10.1111/CRD4.2021240503)).

### 141 *Inclusion and exclusion criteria*

142 For inclusion, studies had to be published between inception and June 15<sup>th</sup>, 2022, and written in  
143 English. Diagnosis of stages of psychosis was established using a recognized clinical assessment  
144 tool (see eMethods for *Clinical Stages* definition). Studies needed to provide measures of the  
145 prevalence of sleep disturbances in individuals at different psychosis stages and/or quantification  
146 of sleep characteristics in these individuals, assessed with PSG, EEG, actigraphy, or self-reports.  
147 Inclusion and exclusion criteria are explained in greater detail in the eMethods.

### 148 *Search strategy*

149 One author (JB) performed the literature search on the Web of Science and PubMed from  
150 inception until June 15<sup>th</sup>, 2022. The description of study search terms is provided in the  
151 eMethods. A manual search of the references of included articles and of relevant prior  
152 reviews/meta-analyses were also performed.

153 The eMethods contain details on study selection and data extraction.

### 154 *Methodological quality appraisal*

155 Quality appraisal was assessed using the Agency for Healthcare Research and Quality (AHRQ)<sup>26</sup>  
156 methodology checklist for cross-sectional/prevalence studies. For additional details, see  
157 eMethods.

158



159

160 *Statistical analysis*

161 Sleep disturbance prevalence was evaluated in three distinct analyses: 1) a pooled cases analysis  
162 of sleep disturbance prevalence aggregating all psychosis stages; 2) a stage-specific cases  
163 analysis of sleep disturbance; and 3) a moderator analysis comparing clinical stages with one  
164 another. We also performed a secondary analysis in a subgroup of studies assessing insomnia.  
165 Sleep disturbance prevalence effect sizes were analyzed as logit transformed values, quantifying  
166 the log odds of sleep disturbance.

167 Sleep architecture and oscillatory alterations were evaluated in three different analyses: 1) a  
168 pooled case-control comparison of each sleep variable aggregating all psychosis stages; 2) a  
169 stage-specific case-control analysis of sleep abnormalities; and 3) a moderator analysis  
170 comparing clinical stages with one another. Sleep architecture and sleep oscillatory parameters  
171 were analyzed as standardized mean differences across groups using the Hedges'  $g$  statistic<sup>27</sup>.  
172 For all hypothesis testing, we used two-sided tests with statistical significance at the  $P < .05$  level.

173 A random effects linear regression model was fitted for each sleep parameter, and calculated  
174 effect sizes were weighted according to inverse variance to account for the variability of each  
175 study<sup>28</sup>. Meta-analysis models were estimated using restricted maximum likelihood estimation  
176 using the *rma* function in the R *metafor* package in R software v. 4.1.0 (method = "PLO" for  
177 prevalence analyses; method = "SMD" for case-control comparisons).

178 The recovery of missing or partial data from studies and the assessment of study heterogeneity  
179 using funnel plots, Cochran's  $Q$  statistic<sup>29</sup>,  $I^2$  statistic<sup>30</sup> and Egger tests<sup>31</sup> are further discussed in  
180 the eMethods.

181 Moderator analyses were conducted to assess the influence of clinical stage (i.e., CHR-P, EP,  
182 and CP), age (i.e., mean age across the study), sex (i.e., proportion of males in the study),  
183 antipsychotic medications (i.e., proportion of each study sample taking antipsychotics) and  
184 positive and negative symptoms severity on sleep parameters using linear mixed effect meta-  
185 analysis models. For each sleep parameter, we regressed the differences between patient and  
186 control groups from the available sample on each moderator variable. For prevalence, we  
187 regressed the log odds of sleep disturbances on each moderator variable. To further investigate  
188 the interactions of age, sex, and medication with staging, we applied linear mixed effect models  
189 regressing sleep parameter differences on age, sex, medication, and positive and negative  
190 symptom severity moderator variables for each stage separately. A threshold of  $P < 0.017$  was  
191 used to establish statistical significance after correcting for multiple comparison for three  
192 explanatory variables (i.e., sex, age, and proportion medicated) using Bonferroni correction. We  
193 also examined the effects of psychotic symptoms (i.e., Positive and Negative Syndrome Scale  
194 [PANSS]), and a Bonferroni corrected P threshold of 0.025 was used to establish statistical  
195 significance.

## 196 Results

197 The initial search yielded 7418 records (Figure 1). After removing duplicates, 4863 publications  
198 were screened, resulting in 236 studies considered for full-text review. Twelve additional articles  
199 were identified through reference checking. After a full-text review, 59 articles were included,  
200 with 21 studies assessing sleep disturbance prevalence in 5135 patients (eTable 1) and 39 studies  
201 measuring sleep alterations subjectively (e.g., sleep quality) and/or objectively (e.g., sleep  
202 architecture and sleep oscillatory measures) in 1575 patients and 977 controls (eTable 2).

### 203 *Prevalence of sleep disturbances and insomnia*

204 The pooled (i.e., combined CHR-P, EP and CP) prevalence of sleep disturbances was 50% across  
205 clinical stages (95% CI 40% to 61%,  $Q = 611.28$ ,  $df = 20$ , Figure 2A). Stage-specific analyses  
206 yielded a sleep disturbance prevalence of 54% in CHR-P (95% CI 40% to 67%,  $Q = 13.66$ ,  $df =$   
207 3), 68% in EP (95% CI 32% to 90%,  $Q = 21.2$ ,  $df = 3$ ), and 44% in CP (95% CI 32% to 57%,  $Q$   
208 = 432.73,  $df = 12$ , Figure 2A); eFigure 1 shows forest plots of individual studies. Furthermore,  
209 prevalence of insomnia as the primary sleep disturbance was 34% (95% CI 24% to 45%) of  
210 pooled cases, 48% (95% CI 37% to 59%) of EP, and 27% (95% CI 20% to 35%) of CP (Figure  
211 2B, see eFigure 2 for individual studies forest plot). Moderator analysis yielded no sleep  
212 disturbance or insomnia differences between clinical stages (eTable 3).

### 213 *Standardized mean differences in sleep quality*

214 Sleep quality was assessed comparing total PSQI scores between clinical and control groups.  
215 Results indicated a significant SMD in pooled cases versus controls (SMD [95% CI] = 1.00  
216 [0.70, 1.30],  $P < 0.001$ ). Each clinical group showed poorer sleep quality compared to controls  
217 (CHR-P vs control: SMD [95% CI] = 1.25 [0.83, 1.67],  $P < 0.001$ ; EP vs control: SMD [95% CI]  
218 = 1.17 [0.33, 2.01],  $P = 0.006$ ; CP vs control: SMD [95% CI] = 0.65 [0.4, 0.89],  $P < 0.001$ ;

219 Figure 3, see eFigure 3 for forest plot of individual studies). Moderator analysis revealed no  
220 PSQI scores differences between different clinical stages (eTable 3).

221 *Standardized mean differences in sleep architecture*

222 Pooled cases had higher effect sizes for sleep onset latency (SMD = 0.96 [0.62, 1.30], P <  
223 0.001), wake after sleep onset (SMD = 0.50 [0.29, 0.71], P < 0.001), number of arousals (SMD  
224 = 0.45 [0.07, 0.83], P = 0.019), Stage 1 NREM sleep (SMD = 0.23 [0.06, 0.40], P = 0.008), and  
225 REM density (SMD = 0.37 [0.14, 0.60], P = 0.002) vs. controls. Conversely, effect sizes were  
226 lower in pooled cases vs control groups for sleep efficiency (SMD = -0.75 [-0.98, -0.52], P <  
227 0.001) and slow wave sleep (SMD = -0.24 [-0.44, -0.03], P = 0.023). Furthermore, total sleep  
228 time, Stage 2 sleep, and REM latency did not differ between groups (Figure 4; eFigures 4-13  
229 contain forest plots of studies for each sleep architecture variable).

230 Stage-specific case-control comparisons revealed no sleep architecture differences in CHR-P vs.  
231 controls. EP had higher sleep onset latency (SMD = 0.72 [0.52, 0.92], P < 0.001), wake after  
232 sleep onset (SMD = 0.62 [0.34, 0.89], P < 0.001), and Stage 1 (SMD = 0.34 [0.15, 0.53], P <  
233 0.001), along with lower total sleep time (SMD = -0.56 [-0.99, -0.12], P = 0.012) and sleep  
234 efficiency (SMD = -0.90 [-1.20, -0.60], P < 0.001) compared to controls. CP showed higher  
235 sleep onset latency (SMD = 1.36 [0.66, 2.05], P < 0.001) and wake after sleep onset (SMD =  
236 0.51 [0.09, 0.93], P = 0.018), combined with lower sleep efficiency (SMD = -0.73 [-1.14, -0.33],  
237 P < 0.001) vs. controls. CP also showed more arousals (SMD = 0.81 [0.30, 1.32], P = 0.002) and  
238 REM density (SMD = 0.48 [0.19, 0.77], P = 0.001) compared to controls. Moderator analysis  
239 revealed more frequent arousals in CP compared to CHR-P (z = 2.24, p = 0.02, eTable 3).

240

241

242 *Standardized mean differences in spindle and slow wave parameters*

243 Pooled cases showed lower spindle density (SMD = -1.06 [-1.50, -0.63],  $P < 0.001$ ), spindle  
244 amplitude (SMD = -1.08 [-1.33, -0.82],  $P < 0.001$ ), and spindle duration (SMD = -1.21 [-1.69, -  
245 0.73],  $P < 0.001$ , Figure 5) compared to controls. Stage-specific case-control comparisons  
246 revealed that spindle parameters were lower in both EC and CP relative to controls (Figure 5, see  
247 eFigures 14-16 for forest plots of individual studies). Furthermore, moderator analysis showed  
248 no differences between EP and CP in spindle density or amplitude (eTable 3) but lower spindle  
249 duration in CP compared to EP ( $z = -3.91$ ,  $p < 0.001$ ).

250 Finally, slow wave density was not altered in patient groups relative to controls (Figure 5;  
251 eFigure 17 contains a forest plot of individual studies for slow wave density).

252 Supplementary Materials contain results for meta-regressions accounting for medication, age,  
253 sex, and positive and negative symptoms (eResults and eTables 4-8), study heterogeneity and  
254 publication bias (eResults, eFigure 18), study quality appraisal (eTables 9-10) and the PRISMA  
255 2020<sup>25</sup> checklist (eTable 11).

256

257

## 258 Discussion

259 This meta-analysis investigated sleep abnormalities across clinical stages of psychosis and  
260 identified both uniformly present and stage-specific sleep disruptions.

261 *Sleep disturbance prevalence is consistently high throughout psychosis stages*

262 Sleep disturbance prevalence has been commonly found to be higher in psychosis compared to  
263 the general population<sup>7,8</sup>, although prior studies reported a variable incidence (21-100%)<sup>9-11</sup>.  
264 Here, we established that sleep disturbances were present in 50% of pooled clinical cases, with  
265 similar prevalence in different psychosis stages, including at-risk individuals. This suggests that  
266 sleep disturbances are not only present throughout the course of psychosis, including before the  
267 manifestation of a psychotic episode, but are also consistently high in each psychosis stage, thus  
268 representing a critical issue that should be addressed in these individuals.

269 *Sleep quality is poor throughout stages of psychosis*

270 Case-control comparisons of self-reported sleep quality indicated poorer subjective sleep quality  
271 in pooled cases and in each clinical stage. Therefore, in addition to sleep disturbances being  
272 common, the intensity of perceived sleep distress is also more severe throughout the course of  
273 psychosis, including CHR-P, corroborating prior meta-analyses of sleep quality in CHR-P<sup>9,19</sup>.  
274 Notably, in CHR-P poorer sleep quality leads to worse negative symptoms<sup>33</sup> and contributes to  
275 predicting transition to psychosis<sup>5</sup>. Together, these findings expose the need to address subjective  
276 sleep complaints throughout the course of psychosis, even in the at-risk stage. It would therefore  
277 be important for primary care and mental health providers to systematically screen for sleep  
278 disturbances and to promote sleep hygiene practices (e.g., abstaining from caffeine, nicotine, and

279 alcohol near bedtime, avoiding napping, and maintaining regular sleep and rise times and  
280 exposure to daylight) in prodromal individuals.

281 *Shared and distinct sleep architecture alterations are present in EP and CP but not in CHR-P*

282 Consistent with prior meta-analyses<sup>15-18</sup>, case-control comparisons of sleep architecture revealed  
283 increased sleep onset latency, wake after sleep onset, number of arousals, Stage 1 sleep and REM  
284 density, along with lower sleep efficiency and slow wave sleep in pooled clinical cases.

285 Prior work furthermore suggested the presence of specific sleep alterations in early stages of  
286 psychosis<sup>10,19</sup>. However, comparisons from at-risk to chronic stages had thus far not been  
287 performed. Here, stage-specific case-control comparisons showed that sleep architecture  
288 abnormalities were absent in CHR-P and driven by EP and CP stages. Altered sleep  
289 characteristics shared among EP and CP included increased sleep onset latency, increased wake  
290 after sleep onset, and reduced sleep efficiency. These findings are consistent with insomnia, as  
291 well as other disturbances including circadian phase delay, which is supported by recent studies  
292 reporting an association between evening chronotype in at-risk<sup>34</sup> and full-blown psychosis<sup>35</sup>.  
293 Together, these results suggest that difficulties in initiating and maintaining sleep first occur in  
294 full-blown psychosis and remain relatively stable throughout the course of the disorder, as none  
295 of the measures worsened in CP vs. EP.

296 EP also showed a reduction in total sleep time and a higher percentage of Stage 1 sleep, a pattern  
297 that was not observed when comparing other clinical stages to their respective control groups. A  
298 plausible interpretation of these findings is that individuals in the early course of psychosis suffer  
299 from considerable sleep loss and overall shallower sleep, a pattern that is furthermore

300 corroborated by the higher rates of insomnia in EP found in this study. Sleep disruptions in these  
301 individuals are also likely involved in psychotic symptomatology, where psychotic experiences  
302 worsen sleep and sleep exacerbates psychotic symptoms<sup>6,36</sup>. From a treatment perspective, early-  
303 course patients may therefore benefit from routine insomnia screening and targeted sleep  
304 interventions, including cognitive-behavioral therapy for insomnia (CBT-I), which is effective in  
305 ameliorating difficulties in initiating and maintaining sleep<sup>37,38</sup>.

306 CP was the only clinical group with more arousals and increased REM density compared to  
307 controls. Higher REM density has been associated with increased suicidality in psychotic  
308 patients<sup>39</sup>, and pharmacological reviews indicated that antipsychotic medications can enhance  
309 REM density, although effects vary between antipsychotic compounds<sup>11,40</sup>. Weight gain is a  
310 frequent side effect of long-term antipsychotic treatment<sup>41</sup> and has been associated with sleep  
311 apnea in schizophrenia<sup>42</sup>. Brief awakenings can help restore airflow in such conditions, which  
312 may account for the increased frequency of arousals in CP. Moderator analyses further indicated  
313 that CP had more arousals compared to CHR-P and that the number of arousals was significantly  
314 affected by medication ( $p=0.001$ ), above and beyond disease effects ( $z=-3.01$  for medication vs.  
315  $z=2.37$  for pooled cases vs. controls). Altogether, these findings indicate that the effects of  
316 antipsychotic medications on sleep should be closely monitored, especially in CP, and proper  
317 medication adjustments (e.g., decrease medication doses, switch to a different compound) should  
318 be considered based on their impact on these sleep patterns.

319

320



321 *Sleep spindles, but not slow waves, are severely altered in EP and CP*

322 Meta-analyses of sleep oscillations revealed no alteration in slow wave parameters in clinical  
323 cases vs. controls. In contrast, decreased spindle density, spindle amplitude, and duration were  
324 observed in pooled cases vs. controls. Stage-specific analyses further indicated that these deficits  
325 were present in both EP and CP and yielded some of the largest effect sizes in case-control  
326 comparisons ( $z=-4.93$  to  $-8.31$ ). Of note, spindle measures could not be assessed in CHR-P, as  
327 only one study reported spindle measures in this group<sup>43</sup>. Moderator analyses further indicated  
328 that CP patients showed a more pronounced reduction of spindle duration compared to EP.  
329 Worsening of spindle deficits in chronic stages of psychosis were also reported by a recent meta-  
330 analysis on sleep spindles<sup>23</sup>, although the clinical groups (schizophrenia, first-episode psychosis,  
331 and familial risk) and spindle measure (spindle density) only partially overlapped with our study.  
332 Furthermore, our moderator analyses revealed considerably larger effect sizes in spindle  
333 measures for case-control comparisons ( $z=-4.93$  to  $-8.31$ ) relative to the effect sizes for the  
334 proportion medicated ( $z=-1.14$  to  $-2.13$ ), and prior studies have consistently shown an absence of  
335 correlation between antipsychotic medication and spindle deficits in chronic patients<sup>44,45</sup>.  
336 Together, these findings indicate that spindle deficits are unlikely to be related to antipsychotic  
337 medications and may represent a neurophysiological biomarker that could be used to monitor the  
338 course of psychotic disorders. Furthermore, given increasing evidence for an association between  
339 spindle deficits and clinical and cognitive dysfunction in individuals with psychosis<sup>24,46</sup>, spindles  
340 may represent a promising target for novel treatment interventions. In this context, non-invasive  
341 brain stimulation has shown promise to restore sleep oscillations, including spindles<sup>47</sup>.

342

343 *Limitations*

344 The current meta-analysis presents some limitations. First, while included studies were selected  
345 based on comparable sleep assessment tools, substantial variability in across-study methodology  
346 remained. This was most pronounced in sleep disturbance prevalence studies, as sleep disorders  
347 were assessed with established diagnostic tools (e.g., DSM criteria for insomnia) in only one  
348 study<sup>48</sup>. Similarly, across-study methods employed to measure sleep oscillations varied  
349 considerably (e.g., manual vs. automated spindle detection, 2-256 electrodes). Notwithstanding  
350 this methodological variability, we reported robust, consistent findings, especially regarding  
351 spindle deficits in clinical vs. control groups. Second, a few of the included studies were rated as  
352 “poor” (N=2), and several were rated as “weak” (N=26). However, the quality of most of these  
353 studies was “good” (N=27) or “excellent” (N=5). Third, some analyses had limited statistical  
354 power. Specifically, pooled sample sizes of clinical groups included larger samples in CHR-P  
355 and CP individuals in prevalence studies, with relatively few prevalence studies in EP.  
356 Conversely, for sleep quality and architecture studies, CHR-P sample sizes were smaller  
357 compared to EP and CP, indicating that objectively measured sleep is understudied in at-risk  
358 populations. The same applied to sleep spindles, which were reported in only one study in CHR-  
359 P<sup>43</sup>. Fourth, due to insufficient data availability, spindles were not stratified into fast and slow  
360 spindles, although some evidence suggests that distinct alterations in these two types of spindles  
361 may occur in psychosis<sup>49</sup> (see eDiscussion). Similarly, while acute psychosis is likely associated  
362 with specific sleep alterations<sup>50,51</sup>, insufficient data was available to incorporate this factor in the  
363 current meta-analysis. Fifth, the sleep assessments presented here were based on cross-sectional  
364 data rather than on longitudinal evaluations. Nonetheless, this meta-analysis represents the most

365 comprehensive effort to date to delineate sleep abnormalities along the course of psychosis, from  
366 at-risk to chronic stages.

### 367 *Conclusion*

368 This study demonstrates that sleep disturbances are highly prevalent throughout the course of  
369 psychosis and that different stages of psychosis show both shared and distinct abnormalities in  
370 sleep quality, sleep architecture, and sleep spindle parameters.

371 Altogether, these findings indicate several prospective research directions. To begin with, future  
372 studies should use standardized, validated tools to report the prevalence of well-established sleep  
373 disorders, as these are common in psychosis but have been rarely assessed in specific clinical  
374 stages of psychosis. Moreover, longitudinal sleep studies following at-risk populations through  
375 illness stages are necessary to further characterize the interplay between sleep abnormalities and  
376 psychosis. To achieve this, research efforts should move beyond conventionally assessed sleep  
377 measures and evaluate different sleep patterns using emerging mobile technologies to assess  
378 sleep in the home environment<sup>3</sup>. Future work is also needed to further delineate sleep alterations  
379 specific to acute and remitted psychosis, as well as the impact of psychotic symptoms severity.  
380 Additionally, future studies should better understand the role of antipsychotic medications and  
381 different medication types throughout different stages of psychosis. Finally, given the pervasive  
382 spindle alterations in EP and CP, an important future direction involves examining spindle  
383 properties from CHR-P<sup>52</sup> to CP stages to determine whether spindle alterations may represent  
384 risk/susceptibility, monitoring, and/or prognostic biomarkers for psychosis. In doing so, studies  
385 should differentiate between fast and slow spindles to accurately delineate psychosis-related

386 sleep alterations. Findings from these studies will help establish sleep as a core clinical target and  
387 research domain from prodromal to early and chronic stages of psychosis.

## 388 Author Contributions

389 *Concept and design:* Fabio Ferrarelli, Ahmad Mayeli, and Joëlle Bagautdinova.

390 *Acquisition, analysis, or interpretation of data:* All authors.

391 *Drafting of the manuscript:* Joëlle Bagautdinova, Ahmad Mayeli, James D. Wilson, Francesco  
392 L. Donati, Fabio Ferrarelli.

393 *Critical revision of the manuscript for important intellectual content:* Nicholas Meyer, Paolo  
394 Fusar-Poli, and Fabio Ferrarelli.

395 *Statistical analysis:* Ahmad Mayeli, James D. Wilson, Rebekah M Colacot, and Nicholas Meyer

396 *Obtained funding:* Fabio Ferrarelli.

397 *Administrative, technical, or material support:* James D. Wilson, Nicholas Meyer, and Fabio  
398 Ferrarelli.

399 *Supervision:* Fabio Ferrarelli.

400

## 401 Funding

402 This study was funded by a National Institute of Mental Health BRAINS R01 MH113827  
403 awarded to FF.

## 404 Acknowledgement

405 Role of funder: The funders had no role in the design and conduct of the study; collection,  
406 management, analysis, and interpretation of the data; preparation, review, or approval of the  
407 manuscript; and decision to submit the manuscript for publication.

408 Access to data and data analysis: The principal investigator (FF) had full access to all the data in  
409 the study and takes responsibility for the integrity of the data and the accuracy of the data  
410 analysis.

## 411 Conflicts of interest

412 The authors have no conflicts of interest to declare that are relevant to the content of this article.

413

## 414 References

- 415 1. Kraepelin E. *Dementia Praecox and Paraphrenia (RM Barclay, Trans.)*. Huntington, NY. Robert  
416 E. Krieger Publishing Company; 1919.
- 417 2. Hou CL, Li Y, Cai MY, et al. Prevalence of Insomnia and Clinical and Quality of Life  
418 Correlates in Chinese Patients With Schizophrenia Treated in Primary Care. *Perspectives in*  
419 *Psychiatric Care*. 2015;53(2):80-86.
- 420 3. Meyer N, Joyce DW, Karr C, et al. The temporal dynamics of sleep disturbance and  
421 psychopathology in psychosis: a digital sampling study. *Psychological Medicine*. Published  
422 online January 12, 2021:1-10. doi:10.1017/S0033291720004857
- 423 4. Yung AR, McGorry PD. The Prodromal Phase of First-episode Psychosis: Past and Current  
424 Conceptualizations. *Schizophrenia Bulletin*. 1996;22(2):353-370.  
425 doi:10.1093/schbul/22.2.353
- 426 5. Ruhrmann S, Schultze-Lutter F, Salokangas RKR, et al. Prediction of psychosis in  
427 adolescents and young adults at high risk: results from the prospective European prediction  
428 of psychosis study. *Archives of general psychiatry*. 2010;67(3):241-251.
- 429 6. Waite F, Sheaves B, Isham L, Reeve S, Freeman D. Sleep and schizophrenia: From  
430 epiphenomenon to treatable causal target. *Schizophrenia Research*. 2020;221:44-56.  
431 doi:10.1016/j.schres.2019.11.014
- 432 7. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality  
433 index: A new instrument for psychiatric practice and research. *Psychiatry Research*.  
434 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4
- 435 8. Tang J, Liao Y, Kelly BC, et al. Gender and Regional Differences in Sleep Quality and  
436 Insomnia: A General Population-based Study in Hunan Province of China. *Sci Rep*.  
437 2017;7(1):43690. doi:10.1038/srep43690

- 438 9. Clarke L, Chisholm K, Cappuccio FP, et al. Sleep disturbances and the At Risk Mental State:  
439 A systematic review and meta-analysis. *Schizophrenia Research*. Published online July 6,  
440 2020. doi:10.1016/j.schres.2020.06.027
- 441 10. Davies G, Haddock G, Yung AR, Mulligan LD, Kyle SD. A systematic review of the nature  
442 and correlates of sleep disturbance in early psychosis. *Sleep Medicine Reviews*. 2017;31:25-  
443 38. doi:10.1016/j.smr.2016.01.001
- 444 11. Cohrs S. Sleep Disturbances in Patients with Schizophrenia. *CNS Drugs*. 2008;22(11):939-  
445 962. doi:10.2165/00023210-200822110-00004
- 446 12. Zaks N, Velikonja T, Parvaz MA, et al. Sleep Disturbance in Individuals at Clinical High  
447 Risk for Psychosis. *Schizophrenia bulletin*. 2022;48:111-121.
- 448 13. Sasidharan A, Kumar S, Nair AK, et al. Further evidences for sleep instability and impaired  
449 spindle-delta dynamics in schizophrenia: a whole-night polysomnography study with  
450 neuroloop-gain and sleep-cycle analysis. *Sleep Medicine*. 2017;38:1-13.
- 451 14. Sahbaz C, Ozer OF, Kurtulmus A, Kirpinar I, Sahin F, Guloksuz S. Evidence for an  
452 association of serum melatonin concentrations with recognition and circadian preferences in  
453 patients with schizophrenia. *Metabolic Brain Disease*. 2019;34(3):865-874.
- 454 15. Meyer N, Faulkner SM, McCutcheon RA, Pillinger T, Dijk DJ, MacCabe JH. Sleep and  
455 Circadian Rhythm Disturbance in Remitted Schizophrenia and Bipolar Disorder: A  
456 Systematic Review and Meta-analysis. *Schizophrenia Bulletin*. 2020;46(5):1126-1143.  
457 doi:10.1093/schbul/sbaa024
- 458 16. Chouinard S, Poulin J, Stip E, Godbout R. Sleep in Untreated Patients With Schizophrenia:  
459 A Meta-Analysis. *Schizophrenia Bulletin*. 2004;30(4):957-967.  
460 doi:10.1093/oxfordjournals.schbul.a007145
- 461 17. Baglioni C, Nanovska S, Regen W, et al. Sleep and mental disorders: A meta-analysis of  
462 polysomnographic research. *Psychological Bulletin*. 2016;142(9):969-990.  
463 doi:10.1037/bul0000053
- 464 18. Chan MS, Chung KF, Yung KP, Yeung WF. Sleep in schizophrenia: A systematic review  
465 and meta-analysis of polysomnographic findings in case-control studies. *Sleep Medicine  
466 Reviews*. 2017;32:69-84. doi:10.1016/j.smr.2016.03.001
- 467 19. Donde C, Jaffiol A, Khouri C, et al. Sleep disturbances in early clinical stages of psychotic  
468 and bipolar disorders: A meta-analysis. *Australian and New Zealand Journal of Psychiatry*.  
469 Published online 2021:00048674211068395. doi:10.1177/00048674211068395
- 470 20. Castelnovo A, Graziano B, Ferrarelli F, D'Agostino A. Sleep spindles and slow waves in  
471 schizophrenia and related disorders: main findings, challenges and future perspectives.  
472 *European Journal of Neuroscience*. 2018;48(8):2738-2758. doi:10.1111/ejn.13815

- 473 21. Manoach DS, Demanuele C, Wamsley EJ, et al. Sleep spindle deficits in antipsychotic-naïve  
474 early course schizophrenia and in non-psychotic first-degree relatives. *Frontiers in human*  
475 *neuroscience*. 2014;8:762.
- 476 22. Kaskie RE, Graziano B, Ferrarelli F. Topographic deficits in sleep spindle density and  
477 duration point to frontal thalamo-cortical dysfunctions in first-episode psychosis. *Journal of*  
478 *psychiatric research*. 2019;113:39-44.
- 479 23. Lai M, Hegde R, Kelly S, et al. Investigating sleep spindle density and schizophrenia: A  
480 meta-analysis. *Psychiatry Research*. 2022;307:114265. doi:10.1016/j.psychres.2021.114265
- 481 24. Ferrarelli F. Sleep Abnormalities in Schizophrenia: State of the Art and Next Steps. *AJP*.  
482 2021;178(10):903-913. doi:10.1176/appi.ajp.2020.20070968
- 483 25. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated  
484 guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
- 485 26. Rostom A, Dubé C, Cranney A, et al. *Appendix D. Quality Assessment Forms*. Agency for  
486 Healthcare Research and Quality (US); 2004. Accessed June 11, 2022.  
487 <https://www.ncbi.nlm.nih.gov/books/NBK35156/>
- 488 27. Hedges LV. Distribution Theory for Glass's Estimator of Effect size and Related Estimators.  
489 *Journal of Educational Statistics*. 1981;6(2):107-128. doi:10.3102/10769986006002107
- 490 28. Lee CH, Cook S, Lee JS, Han B. Comparison of Two Meta-Analysis Methods: Inverse-  
491 Variance-Weighted Average and Weighted Sum of Z-Scores. *Genomics Inform*.  
492 2016;14(4):173-180. doi:10.5808/GI.2016.14.4.173
- 493 29. Higgins JP, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of*  
494 *Interventions*. John Wiley & Sons; 2019.
- 495 30. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-  
496 analyses. *Bmj*. 2003;327(7414):557-560.
- 497 31. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple,  
498 graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629
- 499 32. Fekih-Romdhane F, Nefzi H, Sassi H, Cherif W, Cheour M. Sleep in first-episode  
500 schizophrenia patients, their unaffected siblings and healthy controls: A comparison. *Early*  
501 *Interv Psychiatry*. Published online October 9, 2020. doi:10.1111/eip.13058
- 502 33. Lunsford-Avery JR, Orr JM, Gupta T, et al. Sleep dysfunction and thalamic abnormalities in  
503 adolescents at ultra high-risk for psychosis. *Schizophrenia Research*. 2013;151(1):148-153.
- 504 34. Lunsford-Avery JR, Pelletier-Baldelli A, Korenic SA, et al. Eveningness chronotype  
505 preference among individuals at clinical high risk for psychosis. *Schizophrenia Research*.  
506 2021;236:3-8. doi:10.1016/j.schres.2021.07.034



- 507 35. Linke M, Jankowski KS. Chronotype in individuals with schizophrenia: A meta-analysis.  
508 *Schizophrenia Research*. 2021;235:74-79. doi:10.1016/j.schres.2021.07.020
- 509 36. Chiu VW, Ree M, Janca A, Waters F. Sleep in Schizophrenia: Exploring Subjective  
510 Experiences of Sleep Problems, and Implications for Treatment. *The Psychiatric quarterly*.  
511 2016;87(4):633-648.
- 512 37. Chiu VW, Ree M, Janca A, Iyyalol R, Dragovic M, Waters F. Sleep profiles and CBT-I  
513 response in schizophrenia and related psychoses. *Psychiatry Res*. 2018;268:279-287.  
514 doi:10.1016/j.psychres.2018.07.027
- 515 38. Hwang DK, Nam M, Lee YJG. The effect of cognitive behavioral therapy for insomnia in  
516 schizophrenia patients with sleep Disturbance: A non-randomized, assessor-blind trial.  
517 *Psychiatry Research*. 2019;274:182-188. doi:10.1016/j.psychres.2019.02.002
- 518 39. Keshavan MS, Reynolds CF, Montrose D, Miewald J, Downs C, Sabo EM. Sleep and  
519 suicidality in psychotic patients. *Acta Psychiatrica Scandinavica*. 1994;89(2):122-125.  
520 doi:10.1111/j.1600-0447.1994.tb01498.x
- 521 40. Monti JM, Torterolo P, Pandi Perumal SR. The effects of second generation antipsychotic  
522 drugs on sleep variables in healthy subjects and patients with schizophrenia. *Sleep Medicine*  
523 *Reviews*. 2017;33:51-57. doi:10.1016/j.smr.2016.05.002
- 524 41. Casey DE, Henderson DC, Lindenmayer JP, Banerji MA. Antipsychotic-Induced Weight  
525 Gain and Metabolic Abnormalities: Implications for Increased Mortality in Patients With  
526 Schizophrenia. Published online 2004:15.
- 527 42. Myles H, Myles N, Antic NA, et al. Obstructive sleep apnea and schizophrenia: A systematic  
528 review to inform clinical practice. *Schizophrenia Research*. 2016;170(1):222-225.  
529 doi:10.1016/j.schres.2015.11.014
- 530 43. Purple RJ, Cosgrave J, Vyazovskiy V, Foster RG, Porcheret K, Wulff K. Sleep-related  
531 memory consolidation in the psychosis spectrum phenotype. *Neurobiology of Learning and*  
532 *Memory*. 2020;174. NA
- 533 44. Ferrarelli F, Huber R, Peterson MJ, et al. Reduced sleep spindle activity in schizophrenia  
534 patients. *The American journal of psychiatry*. 2007;164:483-492.
- 535 45. Markovic A, Buckley A, Driver DI, et al. Sleep spindle activity in childhood onset  
536 schizophrenia: Diminished and associated with clinical symptoms. *Schizophrenia research*.  
537 Published online 2020. NA
- 538 46. Manoach DS, Stickgold R. Abnormal Sleep Spindles, Memory Consolidation, and  
539 Schizophrenia. *Annual Review of Clinical Psychology*. 2019;15(1):451-479.  
540 doi:10.1146/annurev-clinpsy-050718-095754

- 541 47. Lustenberger C, Boyle MR, Alagapan S, Mellin JM, Vaughn BV, Fröhlich F. Feedback-  
542 Controlled Transcranial Alternating Current Stimulation Reveals a Functional Role of Sleep  
543 Spindles in Motor Memory Consolidation. *Current Biology*. 2016;26(16):2127-2136.  
544 doi:10.1016/j.cub.2016.06.044
- 545 48. Huang YS, Guilleminault C, Chen CH, Lai PC, Hwang FM. Narcolepsy-cataplexy and  
546 schizophrenia in adolescents. *Sleep Medicine*. 2014;15(1):15-22.
- 547 49. Schilling C, Schlipf M, Spietzack S, et al. Fast sleep spindle reduction in schizophrenia and  
548 healthy first-degree relatives: association with impaired cognitive function and potential  
549 intermediate phenotype. *European Archives of Psychiatry and Clinical Neuroscience*.  
550 2017;267(3):213-224.
- 551 50. Kaskie RE, Gill KM, Ferrarelli F. Reduced frontal slow wave density during sleep in first-  
552 episode psychosis. *Schizophrenia Research*. 2019;206:318-324.
- 553 51. Keshavan MS, Reynolds CF 3rd, Miewald MJ, et al. Delta sleep deficits in schizophrenia:  
554 evidence from automated analyses of sleep data. *Archives of general psychiatry*.  
555 1998;55(5):443-448.
- 556 52. Mayeli A, Wilson JD, Donati FL, LaGoy AD, Ferrarelli F. Sleep spindle alterations relate to  
557 working memory deficits in individuals at clinical high-risk for psychosis. *Sleep*. Published  
558 online August 19, 2022:zsac193. doi:10.1093/sleep/zsac193
- 559
- 560
- 561
- 562
- 563
- 564
- 565
- 566
- 567
- 568
- 569
- 570

571

572

## 573 Figure Legends

574 **Figure 1.** PRISMA workflow of study selection. \*Of note, one study<sup>32</sup> was included in both the  
575 prevalence and sleep architecture analyses.

576

577 **Figure 2.** Forest plots of A) Prevalence of sleep disturbance and B) Prevalence of insomnia in  
578 the pooled clinical groups and each psychosis subgroup. Logit transformation was applied for  
579 analysis and the final pooled logit was back transformed to proportions for ease of interpretation  
580 of the forest plots.

581

582 **Figure 3.** Summary of standardized mean differences in sleep quality as measured by total PSQI  
583 in the pooled clinical groups and each psychosis subgroup.

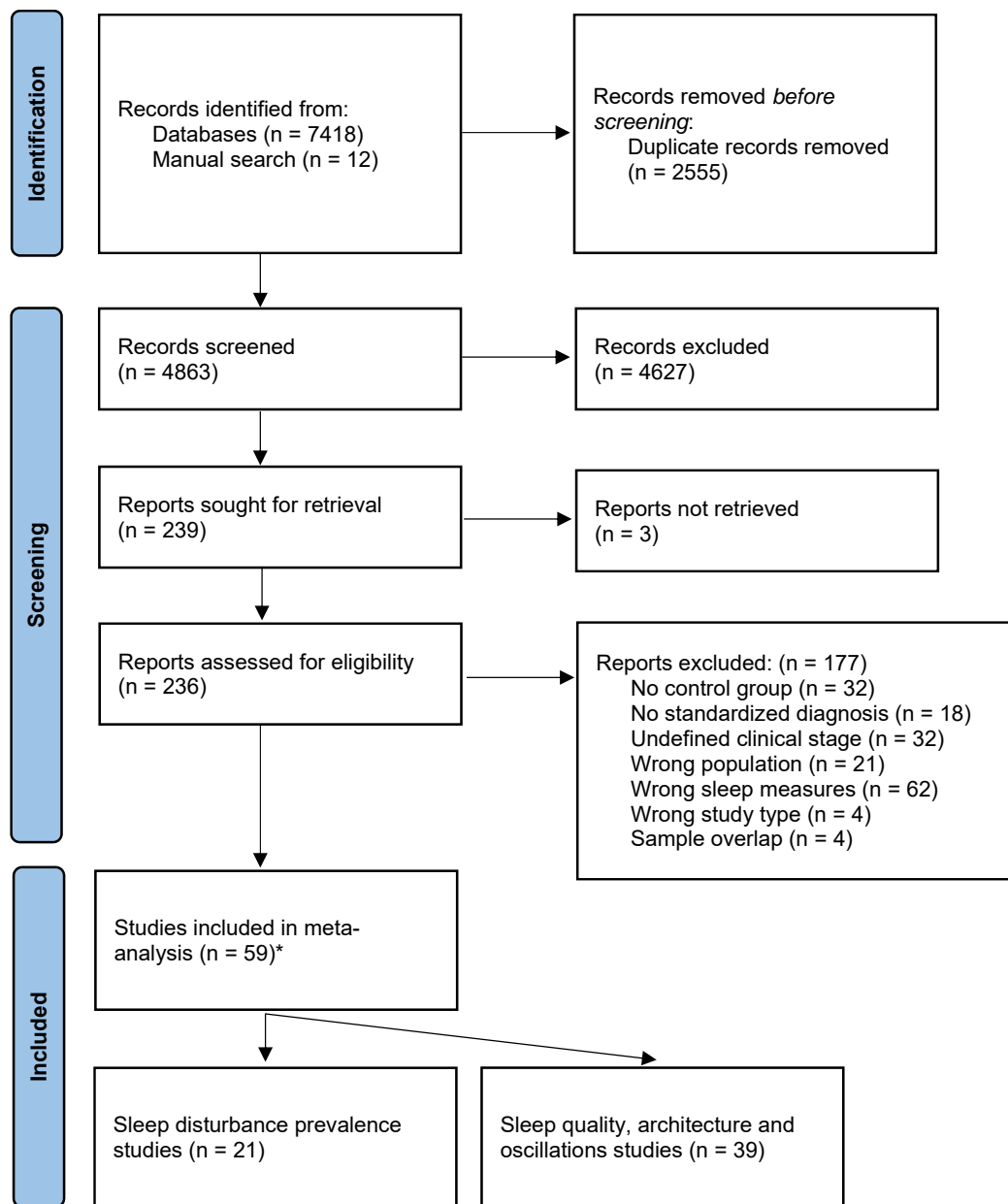
584

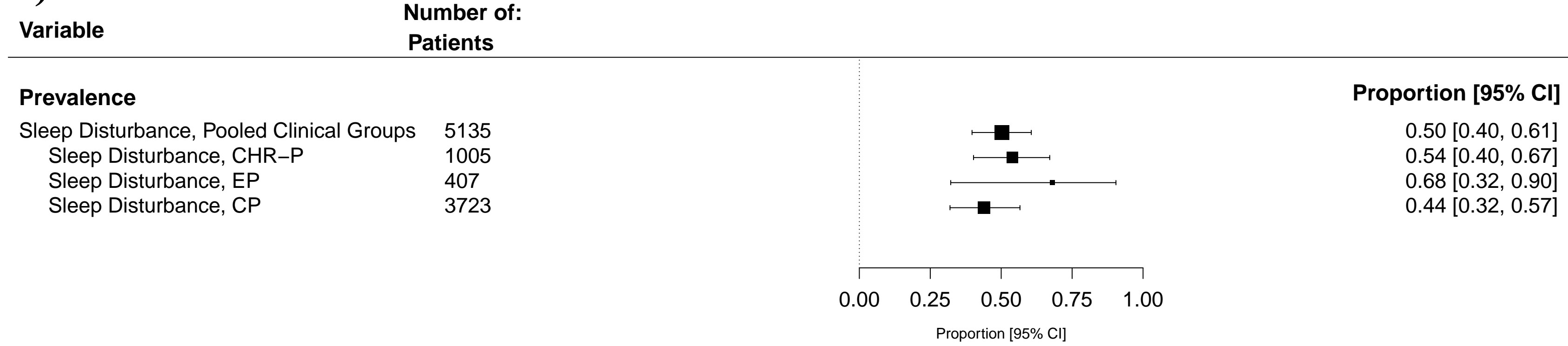
585 **Figure 4.** Summary of standardized mean differences for sleep architecture parameters in pooled  
586 clinical groups and in each clinical subgroup. Significant ( $p < 0.05$ ) effect sizes between two  
587 subgroups are marked with an asterisk.

588

589 **Figure 5.** Summary of standardized mean differences for sleep spindle parameters and slow-  
590 wave density in pooled cases and in each clinical subgroup. Significant ( $p < 0.05$ ) effect sizes  
591 between two subgroups are marked with an asterisk.

592



**A)****B)**