# Sleep for COVID-19: real-time meta analysis of 15 studies

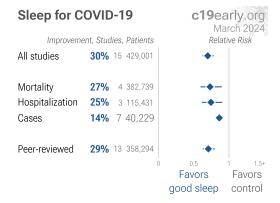
@CovidAnalysis, March 2024, Version 18 https://c19early.org/slmeta.html

#### **Abstract**

Statistically significant lower risk is seen for mortality, hospitalization, and cases. 12 studies from 12 independent teams in 5 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 30% [22-38%] lower risk. Results are similar for peer-reviewed studies.

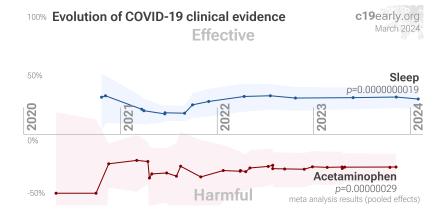
Results are robust — in exclusion sensitivity analysis 13 of 15 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.



Studies analyze sleep quality before infection, and use different definitions of sleep quality.

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis.

All data to reproduce this paper and sources are in the appendix.



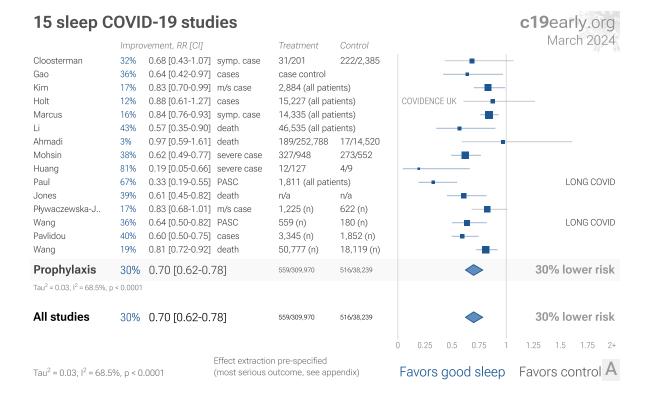
## **HIGHLIGHTS**

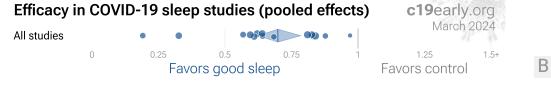
Good quality sleep reduces risk for COVID-19 with very high confidence for mortality, hospitalization, cases, and in pooled analysis.

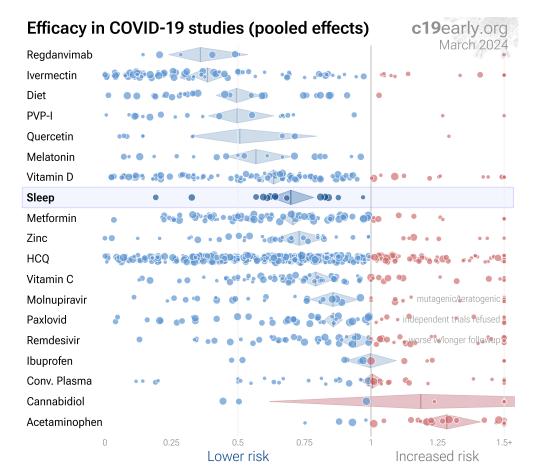
Sleep was the 16th treatment shown effective with  $\ge$ 3 clinical studies in March 2021, now known with p = 0.0000000019 from 15 studies.

We show traditional outcome specific analyses and combined evidence from all studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.







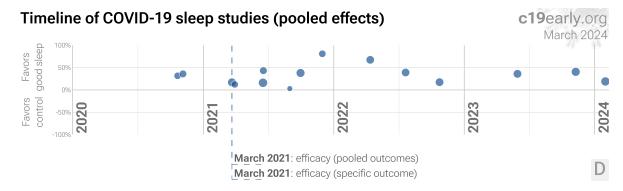


Figure 1. A. Random effects meta-analysis. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. B. Scatter plot showing the most serious outcome in all studies. The diamond shows the results of random effects meta-analysis. C. Results within the context of multiple COVID-19 treatments. 0.6% of 6,686 proposed treatments show efficacy c19early.org. D. Timeline of results in sleep studies. The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes and one or more specific outcome.

## Introduction

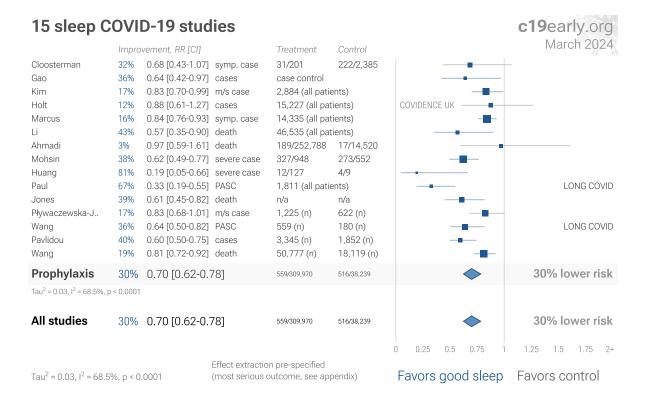
Analysis. We analyze all significant studies reporting COVID-19 outcomes as a function of sleep quality and providing adjusted results. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, individual outcomes, and peer-reviewed studies.

## **Results**

Table 1 summarizes the results for all studies, for peer-reviewed studies, and for specific outcomes. Figure 2, 3, 4, 5, and 6 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, hospitalization, cases, and peer reviewed studies.

	Improvement	Studies	Patients	Authors
All studies	<b>30%</b> [22-38%] ****	15	429,001	146
Peer-reviewed studies	<b>29%</b> [20-37%] ****	13	358,294	134
Mortality	<b>27%</b> [10-40%] **	4	382,739	35
Hospitalization	<b>25%</b> [9-39%] **	3	115,431	30
Cases	<b>14%</b> [7-20%] ****	7	40,229	95

**Table 1.** Random effects meta-analysis for all studies, for peer-reviewed studies, and for specific outcomes. Results show the percentage improvement with good sleep quality and the 95% confidence interval. \*\*\* p<0.01 \*\*\*\*\* p<0.0001.



**Figure 2.** Random effects meta-analysis for all studies with pooled effects. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

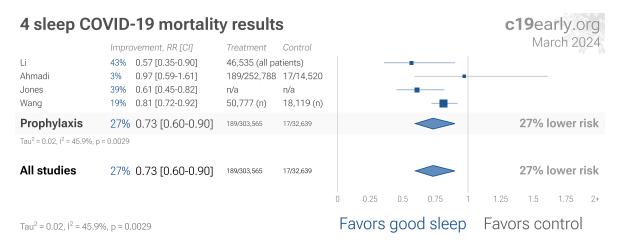


Figure 3. Random effects meta-analysis for mortality results.



Figure 4. Random effects meta-analysis for hospitalization.

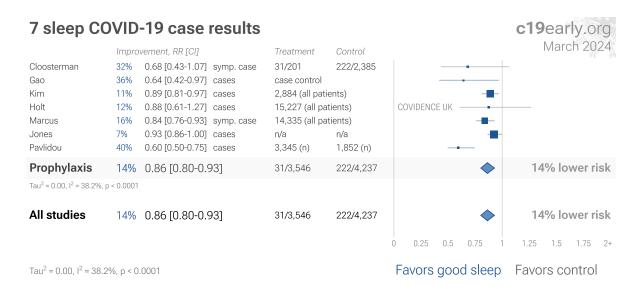
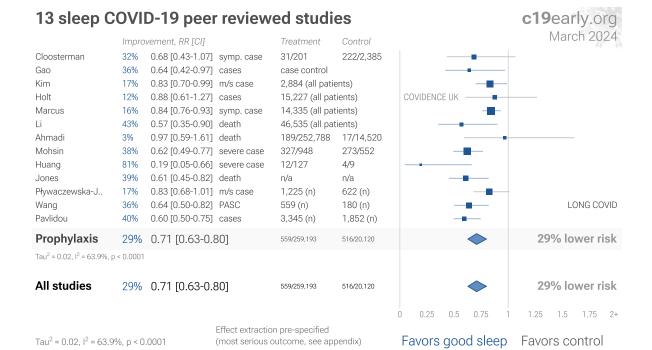


Figure 5. Random effects meta-analysis for cases.



**Figure 6.** Random effects meta-analysis for peer reviewed studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

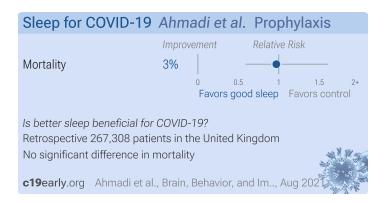
## **Conclusion**

Better sleep reduces risk for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, and cases. 12 studies from 12 independent teams in 5 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 30% [22-38%] lower risk. Results are similar for peer-reviewed studies. Results are robust — in exclusion sensitivity analysis 13 of 15 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

Studies analyze sleep quality before infection, and use different definitions of sleep quality.

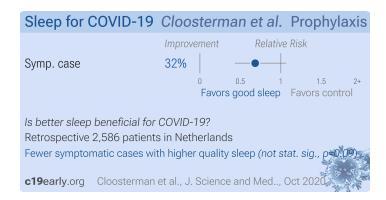
## **Study Notes**

#### Ahmadi



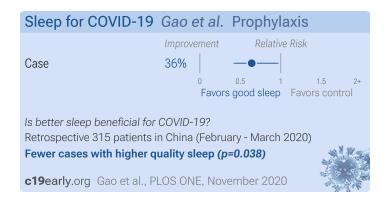
Ahmadi: Retrospective 468,569 adults in the UK, showing no significant difference in COVID-19 mortality based on sleep quality.

#### Cloosterman



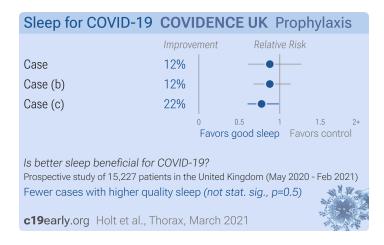
*Cloosterman*: Analysis of 2,586 participants of a running injury prevention RCT in the Netherlands, showing higher risk of COVID-19 symptoms with sleep disturbance.

### Gao



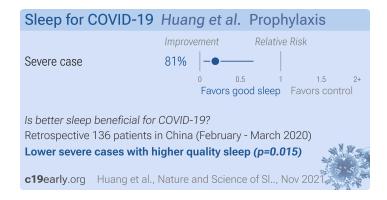
*Gao*: Case control study in China with 105 cases and 210 matched controls, showing COVID-19 cases associated with lack of sleep.

#### Holt



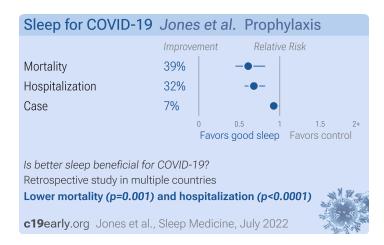
*Holt*: Prospective survey-based study with 15,227 people in the UK, showing reduced risk of COVID-19 cases with 8 hours sleep, with statistical significance when compared with ≥9 hours. NCT04330599. COVIDENCE UK.

#### Huang



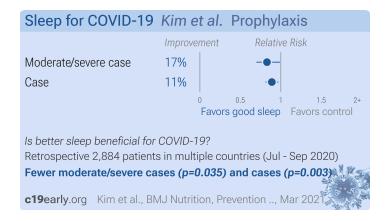
*Huang*: Retrospective 164 COVID-19 patients and 188 controls in China, showing the risk of severe cases associated with lack of sleep.

## **Jones**



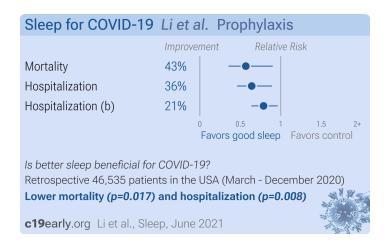
*Jones*: FinnGen Mendelian randomization study showing higher risk of COVID-19 mortality, hospitalization, and infection with insomnia.

#### Kim



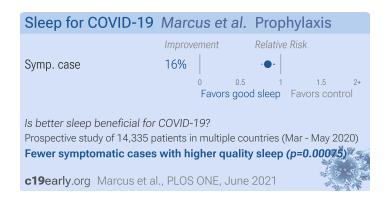
*Kim*: Retrospective 2,884 high-risk healthcare workers in France, Germany, Italy, Spain, UK, and the USA, showing shorter sleep duration associated with increased risk of COVID-19 cases and severity.

#### Li



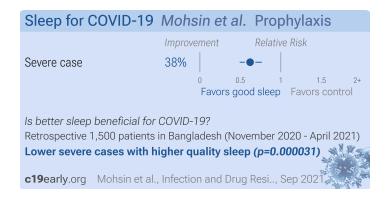
*Li*: UK Biobank retrospective, 46,535 participants with sleep behavior assessed between 2006 and 2010, showing higher risk of hospitalization and mortality with poor sleep.

#### **Marcus**



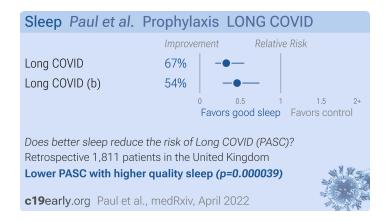
*Marcus*: Prospective survey based study with 14,335 participants, showing risk of viral symptoms associated with shorter sleep duration.

#### Mohsin



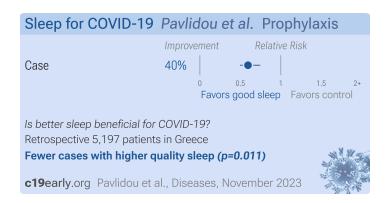
Mohsin: Retrospective 1,500 COVID+ patients in Bangladesh, showing lower risk of severe cases with good sleep.

#### Paul



*Paul*: Retrospective 1,811 COVID-19 patients in the UK, showing lower risk of self-reported long COVID with good sleep quality in the month before infection.

## **Pavlidou**



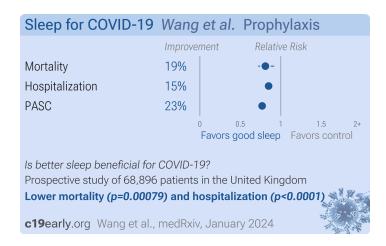
*Pavlidou*: Retrospective 5,197 Greek adults over 65. After adjustment for confounders, COVID-19 infection was independently associated with poor sleep, low physical activity, low Mediterranean diet adherence, living in urban areas, smoking, obesity, depression, anxiety, stress, and poor health-related quality of life.

### Pływaczewska-Jakubowska

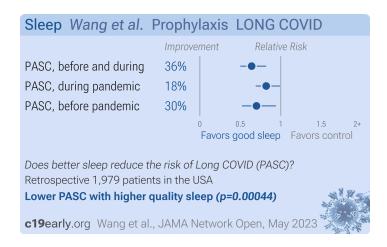


*Pływaczewska-Jakubowska*: Retrospective 1,847 COVID+ patients in Poland, showing lower moderate/severe cases with improved sleep, without statistical significance. Hospitalized patients were excluded.

### Wang



Wang: Prospective study of 68,896 UK Biobank participants with COVID-19 showing adherence to a healthy lifestyle prior to infection, characterized by 10 factors including adequate physical activity and sleep, not smoking, and a healthy BMI, was associated with a significantly lower risk of mortality, hospitalization, and post-COVID multisystem sequelae. Risk decreased monotonically for increasing numbers of healthy lifestyle factors from 5-10. Reduced risks were evident across cardiovascular, metabolic, neurologic, respiratory, and other disorders over 210 days following infection, during both acute and post-acute phases, regardless of age, sex, ethnicity, test setting, vaccination status, or SARS-CoV-2 variant.



Wang (B): Retrospective 1,979 nurses in the USA, showing lower risk of long COVID with better sleep quality.

## **Appendix 1. Methods and Data**

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are sleep AND COVID-19. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of sleep for COVID-19 that report a comparison with a control group are included in the main analysis. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in pooled analysis, while other outcomes are included in the outcome specific analyses. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcomes are considered more important than viral test status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available. After most or all patients have recovered there is little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert to a relative risk according to Zhang. Reported confidence intervals and p-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. When needed, conversion between reported p-values and confidence intervals followed Altman, Altman (B), and Fisher's exact test was used to calculate p-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 Sweeting. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

Forest plots are computed using PythonMeta <sup>Deng</sup> with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I<sup>2</sup> statistic. Mixed-effects meta-regression results are computed with R (4.1.2) using the metafor (3.0-2) and rms (6.2-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a p-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective  $^{McLean, Treanor}$ .

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

A summary of study results is below. Please submit updates and corrections at https://c19early.org/slmeta.html.

### **Prophylaxis**

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. For pooled analyses, the first (most serious) outcome is used, which may differ from the effect a paper focuses on. Other outcomes are used in outcome specific analyses.

Ahmadi, 8/31/2021, retrospective, United Kingdom, peer-reviewed, 5 authors.	risk of death, 3.0% lower, RR 0.97, $p$ = 0.91, adjusted per study, good vs. poor, model 2, multivariable.
Cloosterman, 10/21/2020, retrospective, Netherlands, peer-reviewed, 4 authors.	risk of symptomatic case, 31.6% lower, RR 0.68, $p$ = 0.09, higher quality sleep 31 of 201 (15.4%), lower quality sleep 222 of 2,385 (9.3%), inverted to make RR<1 favor higher quality sleep, odds ratio converted to relative risk.
Gao, 11/5/2020, retrospective, China, peer-reviewed, survey, median age 55.0, 11 authors, study period 10 February, 2020 - 1 March, 2020.	risk of case, 35.9% lower, HR 0.64, $p$ = 0.04, higher quality sleep 73 of 105 (69.5%) cases, 179 of 210 (85.2%) controls, NNT 4.6, inverted to make HR<1 favor higher quality sleep, case control OR, Cox proportional hazards.
Holt, 3/30/2021, prospective, United Kingdom, peer-reviewed, 34 authors, study period 1 May, 2020 - 5 February, 2021, trial NCT04330599 (history) (COVIDENCE UK).	risk of case, 12.3% lower, OR 0.88, $p = 0.50$ , adjusted per study, inverted to make OR<1 favor higher quality sleep, fully adjusted, 8 hours vs. $\leq 6$ hours, RR approximated with OR.
(ilistory) (GOVIDENCE GIV).	risk of case, 12.3% lower, OR 0.88, $p$ = 0.33, adjusted per study, inverted to make OR<1 favor higher quality sleep, fully adjusted, 8 hours vs. 7 hours, RR approximated with OR.
	risk of case, 22.5% lower, OR 0.78, <i>p</i> = 0.04, adjusted per study, inverted to make OR<1 favor higher quality sleep, fully adjusted, 8 hours vs. ≥9 hours, RR approximated with OR.
Huang, 11/30/2021, retrospective, China, peer-reviewed, survey, 5 authors, study period 10 February, 2020 - 28 March, 2020.	risk of severe case, 80.9% lower, RR 0.19, $p$ = 0.02, higher quality sleep 12 of 127 (9.4%), lower quality sleep 4 of 9 (44.4%), NNT 2.9, adjusted per study, inverted to make RR<1 favor higher quality sleep, odds ratio converted to relative risk, recommended vs. lack of sleep, multivariable.

<i>Jones</i> , 7/21/2022, retrospective, multiple countries, peer-reviewed, 12 authors.	risk of death, 39.0% lower, OR 0.61, $p = 0.001$ , inverted to make OR<1 favor higher quality sleep, RR approximated with OR.		
	risk of hospitalization, 32.0% lower, OR 0.68, $p$ < 0.001, inverted to make OR<1 favor higher quality sleep, RR approximated with OR.		
	risk of case, 7.4% lower, OR 0.93, $p = 0.04$ , inverted to make OR<1 favor higher quality sleep, RR approximated with OR.		
Kim, 3/22/2021, retrospective, multiple countries, peer-reviewed, survey, mean age 48.0, 8 authors, study period 17 July, 2020 - 25 September, 2020.	risk of moderate/severe case, 17.0% lower, OR 0.83, $p = 0.03$ , per extra hour of sleep, RR approximated with OR.		
otacy period 17 odry, 2020 20 deptermon, 2020.	risk of case, 11.0% lower, OR 0.89, $p = 0.003$ , per extra hour of sleep, model 3, RR approximated with OR.		
<i>Li</i> , 6/18/2021, retrospective, USA, peer-reviewed, mean age 69.4, 8 authors, study period March 2020 - December 2020.	risk of death, 43.2% lower, OR 0.57, $p$ = 0.02, inverted to make OR<1 favor higher quality sleep, fully adjusted model C, significant poor sleep burden, RR approximated with OR.		
	risk of hospitalization, 35.9% lower, OR 0.64, $p$ = 0.008, inverted to make OR<1 favor higher quality sleep, fully adjusted model C, significant poor sleep burden, RR approximated with OR.		
	risk of hospitalization, 21.3% lower, OR 0.79, $p$ = 0.02, inverted to make OR<1 favor higher quality sleep, fully adjusted model C, moderate poor sleep burden, RR approximated with OR.		
Marcus, 6/17/2021, prospective, multiple countries, peer-reviewed, survey, 12 authors, study period 26 March, 2020 - 3 May, 2020.	risk of symptomatic case, 16.0% lower, OR 0.84, $p$ < 0.001, adjusted per study, per extra hour sleep, multivariable, RR approximated with OR.		
Mohsin, 9/30/2021, retrospective, Bangladesh, peer-reviewed, survey, 10 authors, study period November 2020 - April 2021.	risk of severe case, 37.9% lower, RR 0.62, $p$ < 0.001, higher quality sleep 327 of 948 (34.5%), lower quality sleep 273 of 552 (49.5%), NNT 6.7, adjusted per study, inverted to make RR<1 favor higher quality sleep, odds ratio converted to relative risk, sleep disturbance, multivariable.		
Paul, 4/13/2022, retrospective, United Kingdom, preprint, survey, 2 authors.	risk of long COVID, 67.3% lower, RR 0.33, <i>p</i> < 0.001, adjusted per study, inverted to make RR<1 favor higher quality sleep, odds ratio converted to relative risk, very good/good vs. not good/very poor, multivariable, model 4, control prevalance approximated with overall prevalence.		
	risk of long COVID, 54.0% lower, RR 0.46, $p$ = 0.002, adjusted per study, inverted to make RR<1 favor higher quality sleep, odds ratio converted to relative risk, very good/good vs. average, multivariable, model 4, control prevalance approximated with overall prevalence.		
Pavlidou, 11/9/2023, retrospective, Greece, peer-reviewed, 14 authors.	risk of case, 40.5% lower, OR 0.60, $p$ = 0.01, higher quality sleep 3,345, lower quality sleep 1,852, adjusted per study, inverted to make OR<1 favor higher quality sleep, adequate vs. inadequate sleep, multivariable, RR approximated with OR.		

Pływaczewska-Jakubowska, 10/24/2022, retrospective, Poland, peer-reviewed, median age 51.0, 5 authors, study period May 2020 - January 2022.	risk of moderate/severe case, 17.4% lower, OR 0.83, $p$ = 0.06, higher quality sleep 1,225, lower quality sleep 622, adjusted per study, inverted to make OR<1 favor higher quality sleep, higher quality sleep vs. insomnia or falling asleep after midnight or nightshifts, multivariable, model 3, RR approximated with OR.
	risk of PASC, 7.4% lower, OR 0.93, $p$ = 0.51, higher quality sleep 1,015, lower quality sleep 502, adjusted per study, inverted to make OR<1 favor higher quality sleep, higher quality sleep vs. insomnia or falling asleep after midnight or nightshifts, multivariable, model 3, RR approximated with OR.
Wang, 1/31/2024, prospective, United Kingdom, preprint, 10 authors.	risk of death, 19.0% lower, HR 0.81, $p$ < 0.001, higher quality sleep 50,777, lower quality sleep 18,119, adjusted per study, 7-9 hrs vs. <7 or >9, multivariable.
	risk of hospitalization, 15.0% lower, HR 0.85, $p$ < 0.001, higher quality sleep 50,777, lower quality sleep 18,119, adjusted per study, 7-9 hrs vs. <7 or >9, multivariable.
	risk of PASC, 23.0% lower, HR 0.77, $p$ < 0.001, higher quality sleep 50,777, lower quality sleep 18,119, adjusted per study, 7-9 hrs vs. <7 or >9, multivariable.
Wang (B), 5/30/2023, retrospective, USA, peer-reviewed, 6 authors.	risk of PASC, 36.0% lower, RR 0.64, $p$ < 0.001, higher quality sleep 559, lower quality sleep 180, adjusted per study, healthy sleep before and during the pandemic, multivariable.
	risk of PASC, 18.0% lower, RR 0.82, $p = 0.03$ , adjusted per study, healthy sleep during the pandemic, multivariable.
	risk of PASC, 30.0% lower, RR 0.70, $p$ = 0.02, higher quality sleep 238, lower quality sleep 166, adjusted per study, healthy sleep before the pandemic, sleep score 5 vs. score 0 or 1, multivariable.

# **Supplementary Data**

Supplementary Data

## References

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