

# Effects of non-drug interventions on depression, anxiety and sleep in COVID-19 patients: a systematic review and meta-analysis

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**Abstract.** – **OBJECTIVE:** Patients with Coronavirus Disease 2019 (COVID-19) suffer from anxiety, depression and sleep disorders due to isolation treatment, among other reasons. Whether non-drug interventions can be alternative therapies for COVID-19 patients with anxiety, depression and sleep disorders is controversial. Therefore, we conducted a meta-analysis and systematic review to evaluate the effects of non-drug interventions on anxiety, depression and sleep in patients with COVID-19 to provide guidance for clinical application.

**MATERIALS AND METHODS:** We searched the following databases for randomized controlled trials (RCTs) from December 2019 to July 2020: China Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chongqing VIP Chinese Science and Technology Periodical Database (VIP), Wanfang, Cochrane Library, Web of Science, PubMed, MEDLINE and Embase. Two investigators independently screened the literature according to the inclusion and exclusion criteria, extracted data and evaluated the risk of bias in the included studies. Meta-analysis was performed using RevMan5.3 software.

**RESULTS:** A total of 5 articles with 768 subjects were included. Meta-analysis results indicated that non-drug interventions can reduce anxiety [SMD=-1.40, 95% CI (-1.62, -1.17),  $p<0.00001$ ] and depression [SMD=-1.22, 95% CI (-2.01, -0.43),  $p=0.002$ ] scores in patients with COVID-19. Descriptive analysis indicated that non-drug interventions can improve the sleep status of COVID-19 patients. Sensitivity analysis indicated that the meta-analysis results were stable. Egger's test and Begg's test showed no publication bias.

**CONCLUSIONS:** This meta-analysis found that non-drug interventions can reduce the anxiety and depression scores of patients with

COVID-19. Due to the limitations of this study, more high-quality studies are needed to verify the findings, especially the effect of non-drug interventions on improving the sleep status of COVID-19 patients.

#### Key Words:

Non-drug interventions, Depression, Anxiety, Sleep, COVID-19, Systematic review and meta-analysis.

#### Abbreviations

COVID-19: Coronavirus Disease 2019; RCTs: Randomized controlled trials; CNKI: China National Knowledge Infrastructure; SMD: standardized mean difference; VIP: the Chongqing VIP Chinese Science and Technology Periodical Database; CBM: China biomedical literature database; CIs: confidence intervals; PRISMA: the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

#### Introduction

In December 2019, a case of unexplained pneumonia occurred in Wuhan, Hubei, China, and its clinical manifestations are very similar to viral pneumonia. Subsequent sequencing analysis of lower respiratory tract samples revealed a new coronavirus named Coronavirus Disease 2019 (COVID-19)<sup>1,2</sup>. With the spread of the epidemic, cases have been found in other parts of China and abroad. Now, the patients infected by the novel coronavirus are the main source of infection. Transmission of the virus happens mainly

through respiratory droplets and close contact<sup>3</sup>. Patients diagnosed with this disease must be treated in isolation. Through clinical observation, many patients develop anxiety, depression, and sleep disorders after isolation therapy<sup>4-6</sup>. Anxiety and depression, as a kind of psychological stress, will trigger a series of physiological events, leading to a decline in immunity<sup>7</sup>.

Tang et al<sup>8</sup> found that isolated respondents were more likely to report depression and anxiety symptoms than non-isolated respondents. Wang et al<sup>9</sup> of 1,210 participants from 194 cities in China on the psychological response to the COVID-19 pandemic found that 53.8% of the respondents believed that the outbreak of depression had a moderate or severe psychological impact, 16.5% had moderate to severe depressive symptoms, 28.8% had moderate to severe anxiety symptoms, and 8.1% had moderate to severe stress. Qi et al<sup>10</sup> analyzed the psychological morbidity and fatigue prevalence and related risk factors for COVID-19 patients and found that 43.9% of patients had mental health impairment, 12.2% of patients had symptoms of post-traumatic stress disorder, 26.8% of patients had anxiety and/or depression symptoms, and 53.6% of patients had fatigue symptoms. Therefore, it is very important to alleviate the anxiety and depression of COVID-19 patients and improve sleep.

At present, the commonly used clinical interventions are divided into medical treatment and non-drug interventions. Medical treatment includes sedative drugs, anti-anxiety drugs and hypnotic drugs<sup>11-13</sup>. In general, drug treatment has potential side effects, such as cognitive impairment and the risk of tolerance or dependence<sup>14-16</sup>. There is no tolerance or dependence associated with drugs for non-drug interventions. Therefore, non-drug interventions are often used for patients according to their clinical needs.

However, the effects of non-drug interventions on anxiety, depression, and sleep in COVID-19 patients have not been well confirmed. Considering these inconsistent effects, we conducted a systematic review and meta-analysis of the RCT on this topic to assess the impact of non-drug interventions on COVID-19 patients.

## Materials and Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) guidelines<sup>17</sup> and the recommendations of the Cochrane Collaboration<sup>18</sup>.

### **Registration Protocol**

The protocol of this meta-analysis has been registered on PROSPERO (<https://www.crd.york.ac.uk/prospéro/>). PROSPERO Registration number: CRD42020190466.

### **Literature Screening and Identification of Relevant Studies**

We searched the following databases from December 2019 to July 2020: China Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chongqing VIP Chinese Science and Technology Periodical Database (VIP), Wanfang, Cochrane Library, Web of Science, PubMed, MEDLINE and Embase. The search terms were 2019 novel coronavirus disease, COVID-19, Depression, Anxiety and Sleep. The search method included a combination of free words and MeSH terms.

### **Inclusion Criteria**

(1) Population: patients with COVID-19. (2) Intervention: the interventions were non-drug intervention either alone or in combination with other therapies. The categories of intervention are the modification of patient and caregiver behavior, hospital-based environmental control measures and modification of the home-based environment. We accepted other interventions not specified here as variously defined by individual authors, as long as they did not involve the systemic use of a conventional pharmacological agent. (3) Comparison: the control group was patients who did not receive the abovementioned nonpharmacological intervention or received prophylactic drug treatment. We also included studies comparing two nonpharmacological interventions. When possible, we assessed whether the intervention group and the control group follow the same protocol in other aspects of patient care. We described the interventions adopted by each institute included in the study. (4) Study design: RCTs published in English. (5) Outcome: anxiety, depression and sleep scale.

### **Exclusion Criteria**

The exclusion criteria were as follows: (1) these reports with incomplete data or incorrect data; (2) duplicate studies; (3) case reports, reviews, etc.; and (4) original documents not available.

### Quality Assessment and Data Extraction

Two researchers independently screened the literature and extracted data. If there were differences, the third researcher was asked to judge. Extracted content includes author, publication date, country, sample size, age, type, content and duration of non-pharmaceutical intervention, type of anxiety, depression and sleep quality scale, result measurement data, and intervention time and details.

Cochrane Systematic Evaluation Manual 5.1.0 recommends the bias risk assessment method to assess the risk of bias among the included RCTs. The main items for assessment are as follows: (1) randomization scheme; (2) group hiding; (3) blinding method; (4) incomplete data reporting; (5) selective outcome reporting; and (6) other sources of bias. Each item is categorized as a “high”, “low” or “unclear” risk of bias.

### Data Synthesis and Statistical Analysis

RevMan5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) software was used for meta-analysis. The statistical results of continuity data are expressed as standardized mean difference (SMD). The heterogeneity included in the results of the study was analyzed using the  $\chi^2$  test (the test level was  $\alpha=0.1$ ) and combined with  $I^2$  to quantitatively determine the size of the heterogeneity. When  $p<0.1$  and/or  $I^2>50\%$ , the random effects model is used for the combined analysis; otherwise, the fixed effects model is used for the combined analysis. Sensitivity analysis was performed to identify sources of heterogeneity. Subgroup analysis was performed based on the time of intervention and type of intervention. A funnel chart was drawn to evaluate possible publication bias and small sample bias, including Egger’s test and Begg’s test.

## Results

### Literature Retrieval Results and Basic Features

The flow chart of the literature screening is shown in Figure 1. Five studies<sup>19-23</sup> with 768 subjects were included. All trials were conducted in China and examined non-drug interventions, such as muscle relaxation, respiratory rehabilitation, life intervention, nursing with traditional Chinese medicine and internet-based integrated intervention. Table I and Table II summarize the characteristics of the included studies. The in-

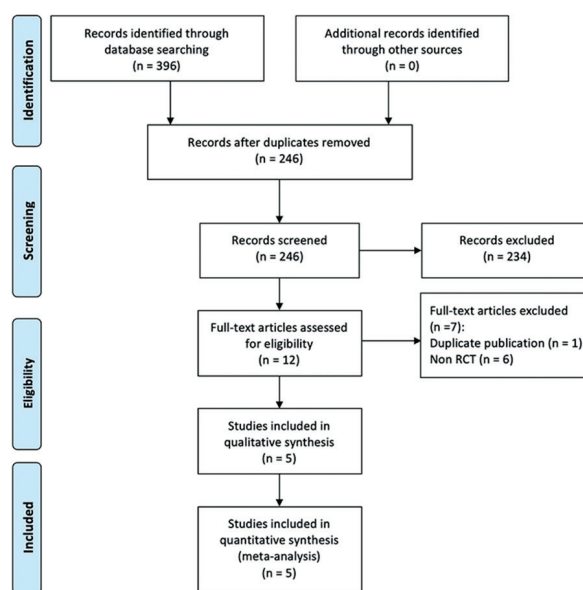
cluded studies were considered to be at a certain risk of bias (Figures 2 to 3) because the participants and interveners had different degrees of bias in blinding, allocation concealment, and random sequence generation. The most commonly used outcome indicators for evaluating anxiety and depression symptoms are the HADS, STAI, SAS, SDS and 17-HAMD. The SRSS was used to measure sleep status. A detailed summary of the results is shown in Table III.

### Symptoms of Anxiety

Five studies<sup>19-23</sup> reported anxiety scores after the intervention. The results of the heterogeneity test were  $I^2=35\%$ ,  $p=0.19$ , indicating the use of a fixed effects model. The meta-analysis results suggested that non-drug interventions can reduce anxiety scores in patients with COVID-19 [SMD=-1.40, 95% CI (-1.62, -1.17),  $p<0.00001$ ], and the difference was statistically significant (Figure 4).

### Symptoms of Depression

Four studies<sup>20-23</sup> reported depression scores after intervention. The results of the heterogeneity test were  $I^2=89\%$ ,  $p<0.00001$ , indicating the use a random effects model. The meta-analysis results suggested that non-drug interventions can reduce depression scores in patients with COVID-19 [SMD=-1.22, 95% CI (-2.01, -0.43),  $p=0.002$ ], and the difference was statistically significant (Figure 5).



**Figure 1.** Flow diagram showing literature filtration process.

**Table 1.** Baseline characteristics of included studies.

Study	Year	State	Period	No. of patients (Start)	No. of atients (End)	Age (years)		Anxiety Measure	Depression Measure	Sleep Measure
						Non-drug intervention group	Control group			
Liu	2020	China	From January 1 to February 16, 2020	51	51	50.41 ± 13.04	50.41 ± 13.04	STAI	NA	SRSS
Liu A	2020	China	From January 1, 2020 to February 6, 2020	76	72	69.4 ± 8.0	68.9 ± 7.6	SAS	SDS	NA
Chen	2020	China	NA	175	175	51.55 ± 18.36	49.23 ± 14.17	SAS	SDS	NA
Chen A	2020	China	NA	60	60	54.03 ± 0.17	54.07 ± 0.15	HAMA	HAMD	NA
Wei	2020	China	From February 2 to February 28, 2020	26	26	40.8 ± 13.5	48.5 ± 9.5	HAMA	17-HAMD	NA

*Abbreviations:* NA, data Not Available; STAI, Spielberger State-Trait Anxiety Scale; SAS, Self-rating anxiety scale; HAMA, Hamilton Anxiety Scale; SDS, Self-rating depression scale; HAMD, Hamilton Depression Scale; 17-HAMD, 17-item Hamilton Depression Scale; SRSS, Sleep State Self-Rating Scale.

**Table II.** Description of interventions.

Study	Yea	Non-drug intervention group		Control group		Duration
		Methods	Frequency	Methods	Frequency	
Liu	2020	Muscle relaxation	Performed this within 20 to 30 minutes each day, training for 5 consecutive days	Routine care	NA	5 d
Liu A	2020	Respiratory rehabilitation	Performed 10 minutes each time, 2 sessions per week for 6 weeks	Without any rehabilitation intervention	NA	6 w
Chen	2020	Life intervention	NA	Routine care	NA	NA
Chen A	2020	Nursing of traditional Chinese medicine	NA	Routine care	NA	NA
Wei	2020	Internet-based integrated intervention	50 minutes a day	Routine care	NA	2 w

Abbreviations: NA, data Not Available; w, week; d, day.

**Symptoms of Sleep**

There was only one study<sup>19</sup> that reported sleep status, so we conducted a descriptive analysis. The results of the descriptive analysis suggested that non-drug interventions can improve patients’ sleep status, SMD=-1.84, 95% CI (-2.51, -1.18),  $p<0.00001$ .

**Subgroup Analysis**

According to the meta-analysis program registered on PROSPERO, a subgroup analysis should be conducted on the types of interventions and

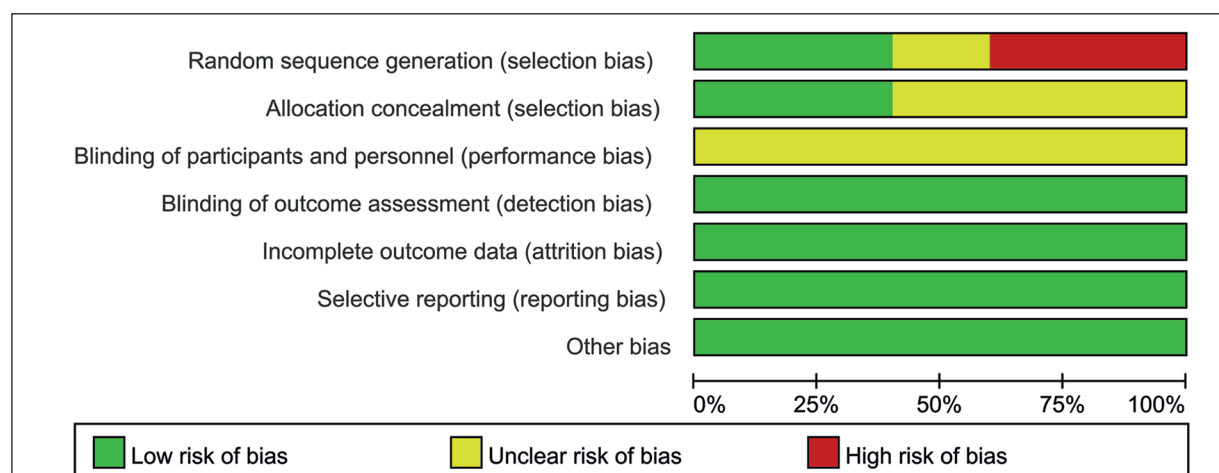
the duration of interventions. However, due to the limited information provided in the included literature, subgroup analysis was not possible.

**Sensitivity Analysis**

Sensitivity analysis suggested that the results of this meta-analysis were robust, as shown in Figure 6-7.

**Publication Bias**

We used Egger’s test and Begg’s test to assess publication bias. It was found that there was no



**Figure 2.** Risk of bias graph.



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen 2020	?	?	?	+	+	+	+
Chen A 2020	+	?	?	+	+	+	+
Liu 2020	-	?	?	+	+	+	+
Liu A 2020	-	+	?	+	+	+	+
Wei 2020	+	+	?	+	+	+	+

Figure 3. Risk of bias summary.

publication bias with respect to anxiety (Egger’s test,  $p=0.111$ ; Begg’s test,  $p=0.327$ ) or depression (Egger’s test,  $p=0.823$ ; Begg’s,  $p=0.174$ ) (Figure 8 and 9).

### Discussion

Both the COVID-19 disease itself and the enclosed environment of isolation wards can have adverse psychological effects on patients<sup>24,25</sup>. During hospitalization, patients leave their familiar working and living environment and are isolated. Their normal lifestyle is completely disrupted. In addition, the monotonous life in the isolation ward and the lack of recreational activities lead to psychological disorders. Psychological disorders weakened a patient’s immunity and reduce treatment enthusiasm; both of them have negative impacts on the rehabilitation of the disease<sup>19</sup>.

The purpose of this systematic review and meta-analysis was to organize and analyze relevant literature on the effects of non-drug interventions on anxiety, depression and sleep in COVID-19 patients. The meta-analysis results showed that non-drug interventions can reduce the anxiety and depression scores of COVID-19 patients. Descriptive analysis showed that non-drug interventions can improve the sleep status of COVID-19 patients. In the absence of adverse reactions, medical staff can combine non-drug interventions with daily medical care to optimize the treatment of anxiety and depression in COVID-19 patients.

The findings in this systematic review were consistent with the previously published systematic review of the effects of non-drug interventions on reducing anxiety and depression in patients with chronic obstructive pulmonary disease (COPD)<sup>26</sup>. There were five main types of non-drug interventions involved in this meta-analysis. Muscle relaxation is a method of deep muscle relaxation. The principle is that muscle tone is the body’s physiological response to stimulating thinking<sup>27</sup>. This is especially true for the relief of anxiety symptoms in young women<sup>28</sup>, prenatal anxiety<sup>7</sup>, and early breast cancer patients<sup>29</sup>. Respiratory muscle-related rehabilitation training in respiratory rehabilitation training plays an important role in maintaining respiratory function. Liu et al<sup>20</sup> have shown that respiratory rehabilitation can significantly improve respiratory function, quality of life, anxiety and depression in elderly patients with COVID-19 and non-COPD patients. The current popularity of Internet and smartphones has greatly increased the efficiency of mental health services in the COVID-19 epidemic. Wei et al<sup>21</sup> have shown that integrated network-based psychological intervention can effectively improve the emotional symptoms of patients with new coronary pneumonia accompanied by symptoms of depression and anxiety, and it is more convenient for patients to be isolated and reduces the chance of infection exposure of psychologists. A good lifestyle and diversified hospital activities are helpful for patients to adapt to the hospital environment and are of great significance for improving the quality of life of patients and promoting physical and mental recovery. Chen et al<sup>22</sup> used life intervention to intervene in patients with new coronavirus pneumonia and, as a result, reduced the anxiety and depression of patients with new coronavirus pneumonia and

**Table III.** Outcome data summary.

Outcome	Instrument	Study	Year	Non-drug intervention group				Control group			
				No. of Patients	Baseline	No. of Patients	Post-treatment	No. of Patients	Baseline	No. of Patients	Post-treatment
Anxiety	STAI	Liu	2020	25	57.88 ± 11.51	25	44.96 ± 12.68	26	56.92 ± 7.92	26	57.15 ± 9.24
	SAS	Liu A	2020	38	56.3 ± 8.1	36	47.4 ± 6.3	38	47.4 ± 6.3	36	54.9 ± 7.3
	HAMA	Wei	2020	13	10.29 ± 1.89	13	3.51 ± 1.28	13	10.87 ± 2.04	13	7.45 ± 1.97
	SAS	Chen	2020	75	55.21 ± 9.88	75	32.29 ± 9.60	100	53.32 ± 11.76	100	45.73 ± 8.58
Depression	HAMA	Chen A	2020	30	16.02 ± 6.18	30	8.92 ± 1.57	30	16.05 ± 6.15	30	16.07 ± 6.14
	SDS	Liu A	2020	38	56.4 ± 7.9	36	54.5 ± 5.9	38	55.9 ± 7.3	36	55.8 ± 7.1
	17-HAMD	Wei	2020	13	9.78 ± 1.87	13	2.48 ± 0.74	13	10.34 ± 9.43	13	7.16 ± 2.04
	SDS	Chen	2020	75	44.37 ± 6.56	75	35.75 ± 9.13	100	46.46 ± 7.83	100	43.33 ± 10.21
Sleep	HAMD	Chen A	2020	30	16.11 ± 6.36	30	8.65 ± 1.48	30	16.09 ± 6.40	30	16.08 ± 6.37
	SRSS	Liu	2020	25	24.04 ± 3.87	25	16.76 ± 4.10	26	23.85 ± 2.82	26	23.23 ± 2.70

*Abbreviations:* STAI, Spielberger State-Trait Anxiety Scale; SAS, Self-rating anxiety scale; HAMA, Hamilton Anxiety Scale; SDS, Self-rating depression scale; HAMD, Hamilton Depression Scale; 17-HAMD, 17-item Hamilton Depression Scale; SRSS, Sleep State Self-Rating Scale.

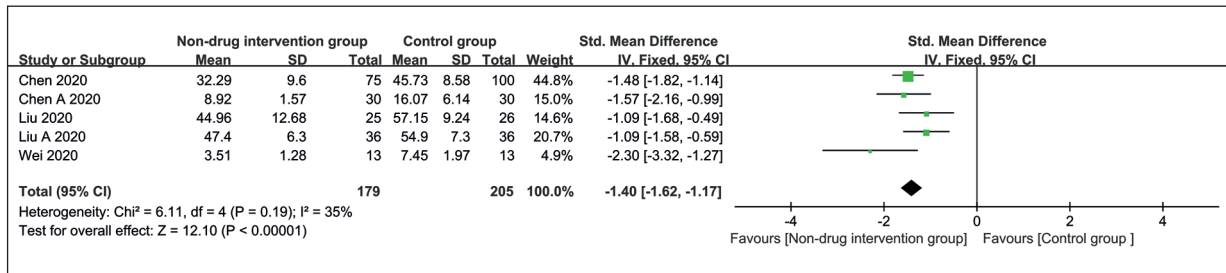


Figure 4. Pooled effect of non-drug interventions compared with control on symptoms of anxiety in people with COVID-19.

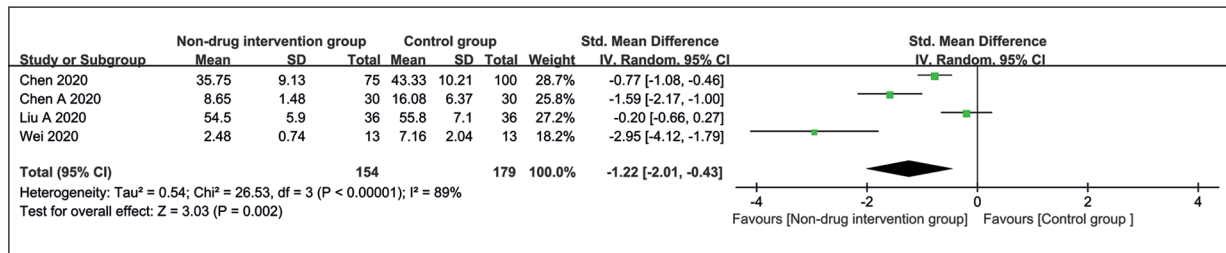


Figure 5. Pooled effect of non-drug interventions compared with control on symptoms of depression in people with COVID-19.

improved their quality of life. Chinese medicine in our country plays an important role in the prevention and treatment of this epidemic, and Chinese medicine nursing technology also has a significant effect on regulating the body's immunity. Chen et al<sup>23</sup> found that the application of Chinese medicine nursing intervention is beneficial to improve the negative psychological emotion of patients with COVID-19. There are various forms of non-drug interventions that can

avoid or reduce the negative effects of negative emotions on patients. This method usually has the advantages of low cost, easy implementation, and small adverse reactions. When clinical staff choose non-drug interventions to intervene in patients with COVID-19, they need to formulate individual and diversified non-drug interventions based on local conditions to achieve early intervention and promote patients' physical and mental health.

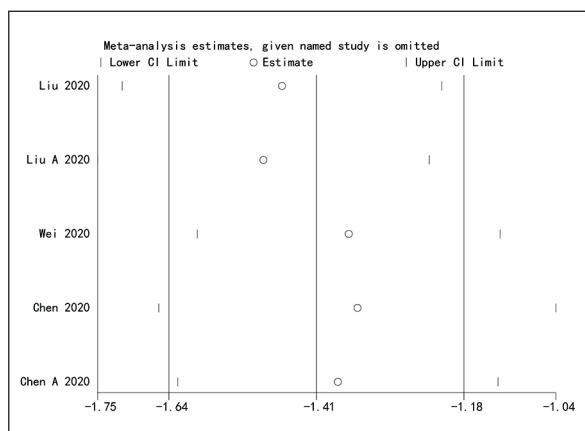


Figure 6. Sensitivity analysis of non-drug interventions compared with control on symptoms of anxiety in people with COVID-19.

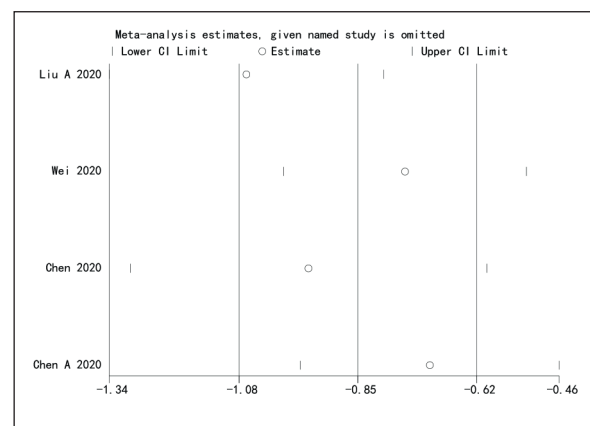
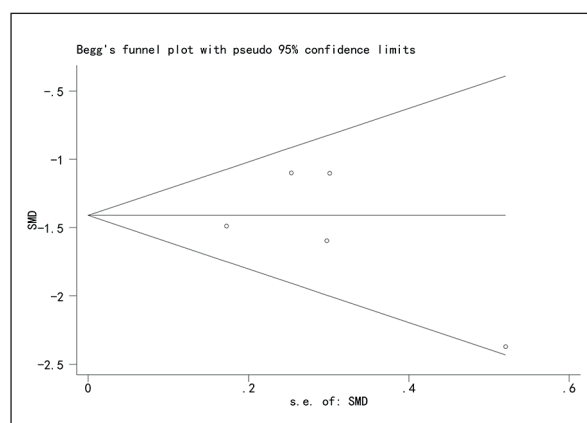
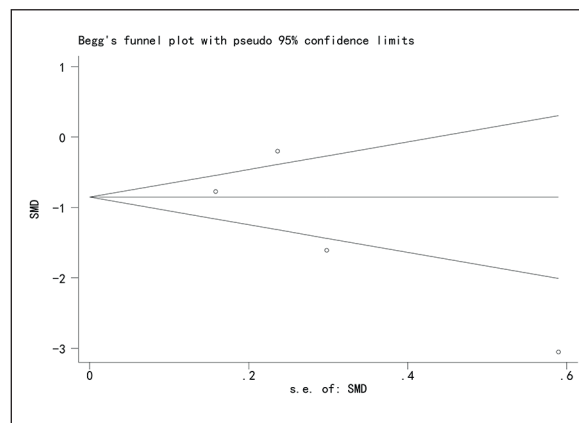


Figure 7. Sensitivity analysis of non-drug interventions compared with control on symptoms of depression in people with COVID-19.





**Figure 8.** Begg's funnel plot of non-drug interventions compared with control on symptoms of anxiety in people with COVID-19.



**Figure 9.** Begg's funnel plot of non-drug interventions compared with control on symptoms of depression in people with COVID-19.

### Limitations

This study has some limitations. This study only searched Chinese and English databases, and there may be incomplete searches and inclusions. In this meta-analysis, there were few studies that can carry out meta-analysis, and the information provided in the literature was limited. We could not perform subgroup analysis. There are various methods of non-drug interventions, and the differences in the intervention processes and the flaws in the trial designs may have led to heterogeneity in the results.

### Conclusions

This meta-analysis further strengthened the positive effects of non-drug interventions on anxiety and depression in COVID-19 patients. However, the research flaws included in the experimental designs also affected the results. Therefore, it is necessary to design more scientific and feasible randomized controlled trials to prove the effectiveness of non-drug interventions on anxiety and depression in patients with COVID-19, especially the improvement of sleep status.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Acknowledgements

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### Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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