

# Chapter 4

## Psychological Distress Impact of Coronavirus Disease (COVID-19) Outbreak on Three Continents: A Systematic Review and Meta-analysis



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### Abstract

*Background:* The dire state of coronavirus disease (COVID-19) outbreak has had a substantial psychological impact on society.

*Methods:* A systematic search was performed through Medline, PubMed, Embase, Scopus, and Web of Science, to investigate the impact of the COVID-19 pandemic on the psychological health of individuals in various countries. Subgroup analyses considered gender and classification of countries into three continents of America, Europe, and Asia. Only studies that used the COVID-19 Peritraumatic Distress Index (CPDI) questionnaire as a tool to assess mental distress were included

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in this meta-analysis. Heterogeneity among studies was assessed by  $I^2$  statistic, and the random-effects model was utilized to obtain the pooled prevalence.

**Results:** This pooled analysis included a large data sample of 21 studies consisting of 94,414 participants. The pooled prevalence of the psychological distress during the time of COVID-19 pandemic by CPDI for the continent of Asia was 43% (34.6% mild-to-moderate and 8.4% severe) which was greater than that for Europe (35%; 30% mild-to-moderate and 5% severe) but lower than that for America (64.3%; 45.8% mild to moderate and 18.5% severe). In addition, the prevalence of psychological distress according to CPDI was higher in females (48%; 40% mild to moderate, 13% severe) compared with males (59%; 36% mild to moderate and 5% severe).

**Conclusions:** Our findings suggest that psychological distress in the Americas is a larger problem than in Asia and European continents. Females appear to be more vulnerable and may therefore require further attention in terms of preventive and management strategies. Implementation of both digital and molecular biomarkers is encouraged to increase objectivity and accuracy of assessing the dynamic changes in mental health in the current and future pandemics.

**Keywords** COVID-19 · SARS-COV-2 · Anxiety · Depression · Psychological distress · Posttraumatic stress syndrome

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## 1 Introduction

Coronavirus 2019 (COVID-19) was declared a pandemic after reaching more than 140 thousand cases by the World Health Organization (WHO) on March 11, 2020 [1]. The virus has since spread worldwide rapidly through several waves and emergence of numerous variants and reached more than 620 million cases with 6.5 million deaths by October 2022 [2]. Naturally, pandemics such as this coronavirus have a long-standing history of affecting physical and mental health in all demographic groups [3, 4].

To control and reduce the prevalence of the virus and save human lives, various strategies have been followed in the world, one of the most important being the different lockdown and quarantine approaches [5]. Over one-third of the global population has experienced periods of these steps, which has even been extended in some countries [6]. Due to these policies, the COVID-19 pandemic has had an unprecedented psychological effect on people from all walks of life [7]. While in quarantine, patients with confirmed or suspected COVID-19 disease can experience high levels of anxiety, depression, stress, fear, boredom, isolation, insecurity, posttraumatic stress (PTS) symptoms, confusion, and stigma, all of which are signs of psychological distress [8, 9].

Due to the rapid and evolving nature of this health emergency during the first year of the pandemic, a number of studies on associated emerging mental health problems have been published [10–16]. It is hoped that such analyses can help to prepare us from new outbreaks of the COVID-19 as well as in the likely event of future pandemics. For these reasons, we have updated these previous reports by conducting a systematic review and meta-analysis of studies published on a global prevalence of the psychological distress impact of COVID-19 pandemic in different countries. In addition, subgroup analyses were conducted to consider the effects of gender and regional distribution across three continents of North America, Europe, and Asia. In addition, we propose a route forward in preparedness for the future pandemics using a combination of psychological and molecular screening tools to aid in patient risk assessment.

## 2 Materials and Methods

### 2.1 Database and Search Strategy

We developed a protocol according to the PRISMA guidelines [17]. Published papers indexed in Medline-PubMed, Embase, Web of Science, and Scopus were searched using the following MeSH terms and keywords: “coronavirus diseases 19,” OR “SARS-CoV-2,” OR “COVID-19,” AND “psychological distress,” AND “prevalence”, AND “COVID-19 per traumatic Distress Index,” alone or combination. For preprint articles, we searched medRxiv and the Social Science Research Network (SSRN) COVID-19 Research Topic. References from selected articles were inspected to detect additional potential studies.

## 2.2 Eligibility Criteria

We selected studies that (a) reported psychological distress due to COVID-19, (b) used the COVID-19 Peritraumatic Distress Index (CPDI) questionnaire for the evaluation of psychological distress, (c) were published in English language, (d) were published between January 1, 2020 to January 1, 2021, and (e) were available as full texts. We excluded (a) interventional studies, (b) studies with incomplete or unclear methods/data, and (c) non-original or duplicate studies.

## 2.3 Introducing the CPDI

CPDI is an instrument for the evaluation of specific phobias and stress disorders due to COVID-19. This questionnaire was originally developed in Chinese [10] and then validated and used in many countries around the world. The 24-item CPDI questionnaire is designed in the form of 5-point Likert-type (0 “never,” 1 “occasionally,” 2 “sometimes,” 3 “often,” 4 “most of the time”). Items in the questionnaire inquire about the frequency of anxiety, depression, specific phobias, cognitive change, avoidance and compulsive behavior, physical symptoms, and loss of social functioning with a range from 0 to 100 and a higher final score indicating higher distress. A score  $\leq 27$  indicated normal distress, between 28 and 51 indicated mild-to-moderate distress, and a score  $\geq 52$  indicated severe distress [10].

## 2.4 Data Extraction

After obtaining full texts of relevant articles, two authors (SA and FRB) independently abstracted all studies using a pre-designed form. Inconsistencies between the two reviewers were adjudicated by a third independent reviewer (AVA). The data elements included the name of the first author (or authors if only two are listed), year of publication, place of study (country), population, sample size, study design, gender, age, number of individuals with normal, mild-to-moderate and severe psychological distress based on CPDI scores, and division of studies by country into three continents: The Americas (North and South America counted as one continent), Europe, and Asia which include Middle East countries.

## 2.5 Quality Assessment

Quality assessment of studies was conducted using the National Institutes of Health (NIH) tool [18]. This consists of 14-item questions and was used for observational cohort and cross-sectional studies. Items in the questionnaire inquired about the

research question (Q1), study population (Q2 and Q3), eligibility criteria (Q4), sample size justification (Q5), outcome measurement (Q6), timeframe sufficient (Q7), exposure of interest (Q8), exposure measures and assessment (Q9), repeated exposure assessment (Q10), outcome measures (Q11), blinding of outcome assessors (Q12), follow-up rate (Q13), and statistical analyses (Q14). The details of these questions are available at supplementary file as footnote of Supplemental Table S1. After evaluating all components of any given study and based on the number of “yes” responses, a rating of good (7–9), medium (4–6), or poor ( $\leq 3$ ) was determined for each study [19]. Studies with a poor rating were excluded from the meta-analysis. Two reviewers (SA and FRB) assessed the quality of studies and disagreements between them was resolved with the final judgement offered by the senior investigator (AVA). The inter-rater agreement in ratings was also calculated, and the final rate of quality of included studies based on the number of “yes” according to inter-rater agreement is presented in Supplemental Table S1.

## 2.6 Statistical Analysis

We obtained the globally pooled prevalence for normal, mild-to-moderate, and severe psychological distress based on CPDI scores with confidence intervals (CI) for each study. Prevalence was calculated assuming binomial distribution. In addition, we calculated prevalence of normal, mild-to-moderate, and severe psychological distress for subgroups including gender (females versus males) and continent (Americas, Europe, and Asia). For analyses of pooled prevalence and CI, a random-effects model was used. Heterogeneity among studies was assessed using the I<sup>2</sup> index, for which values  $>70\%$  represented a high heterogeneity. When the data were homogeneous, a fixed-effects model was used, while a random-effects model was employed when the heterogeneity source was unknown. Publication bias was determined through visual inspection of a funnel plot. Additionally, to assess the bias, Egger’s [20] and Begg’s [21] tests were conducted. All analyses were performed using the STATA software (v16.0; College Station, TX, USA), and significant levels were set at  $p < 0.05$ .

## 3 Results

### 3.1 Search Outcomes

The search strategy yielded 2707 articles. After removal of duplicates ( $n = 668$ ), a careful assessment of the title and abstracts resulted in the elimination of 1932 articles as they did not meet the inclusion criteria. Following examination of the reference lists of related articles, 8 studies were added, and 95 full text articles were assessed for eligibility. Of these, 74 full text articles were excluded because (1)

prevalence was reported as a mean instead of a proportion ( $n = 29$ ), (2) prevalence was not reported ( $n = 18$ ), (3) the methodology was unclear or of low quality ( $n = 19$ ), and (4) it was a review article ( $n = 8$ ). This left a final 21 articles that met our criteria and were included in the meta-analysis. These 21 studies comprised a total number of 94,414 participants, which included 5 studies with 5532 participants in the Americas [22–26], 6 with 27,269 participants in Europe [13, 26–32], and 10 with 61,613 participants in Asia [10–12, 33–39]. The PRISMA flowchart of study selections for the systematic review along with the reasons for exclusion is presented in Fig. 4.1.

### 3.2 Study Characteristics

The characteristics of studies included in the meta-analysis are presented in Table 4.1. The majority of studies were cross-sectional in nature and conducted during the period of the COVID-19 pandemic between January 2020 and January 2021. Out of the 21 studies, 10 were from Asia (including the Middle East) (1 from China, 1 from Iran, 1 from Saudi Arabia, 2 from India, 2 from Nepal, 1 from Egypt, 1 from Philippines, and 1 from Bangladesh), 6 from Europe (5 from Italy and 1 from Germany), and 5 from the Americas (1 from USA, 1 from Peru, and 3 from Brazil). All studies used the CPDI tool for assessment of psychological distress. Out of 21 studies, 15 were performed across the general population and 3 were on child welfare workers [22], students [24], and endodontists [36]. The study from Egypt estimated the prevalence of psychological distress based on CPDI among the general population and healthcare workers separately [39]. Two of the papers were designed as case-control studies on adults with autoimmune arthritis [27] or with cystic fibrosis [31], both compared to the general population. The mean age of study participants ranged from 32.0 to 57.7 years. The sample sizes in the studies varied from 45 to 52,730. Seventeen studies were of good quality and 4 were of medium quality based on use of the NIH tool.

### 3.3 Pooled Prevalence of Psychological Distress

Psychological distress was estimated using CPDI scores into normal, mild-to-moderate, and severe across categories as detailed in the methods section. We estimated the pooled prevalence of each category separately over the 21 studies with a sample size 94,414. The pooled prevalence percentages of the determined normal (Fig. 4.2), mild-to-moderate (Fig. 4.3a), and severe (Fig. 4.3b) psychological distress groups were 55% (95% CI: 47–63%,  $I^2 = 98.97%$ ,  $p < 0.001$ ), 36% (30–41%,  $I^2 = 97.42%$ ,  $p < 0.001$ ), and 10% (6–13%,  $I^2 = 93.39%$ ,  $p < 0.001$ ), respectively.

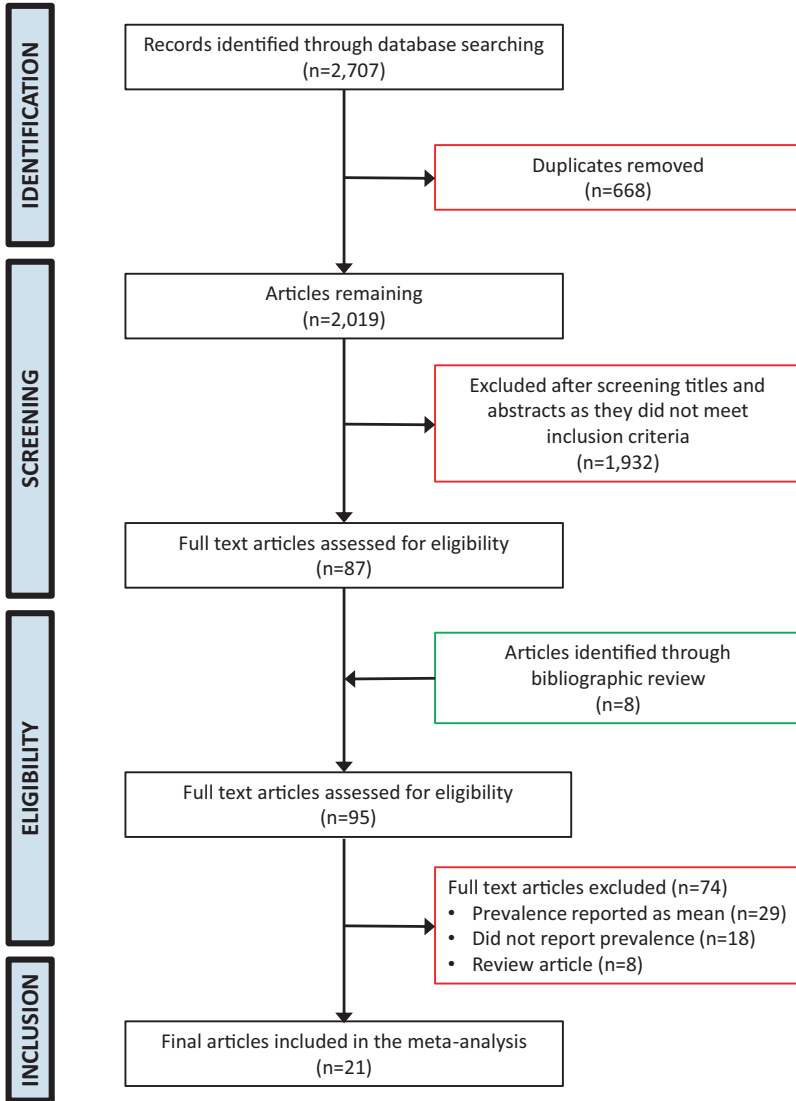


Fig. 4.1 PRISMA flowchart showing the selection of studies

### 3.4 Pooled Prevalence of Psychological Distress According to Continents

The normal, mild-to-moderate, and severe pooled prevalence percentages of psychological distress in the 5 studies from the Americas (sample size = 5532) were estimated at 35.7% (19.7–51.8%,  $I^2 = 96.99%$ ,  $p < 0.001$ ), 45.8% (39.8–51.8%,  $I^2 = 77.78%$ ,  $p < 0.001$ ), and 18.5% (8–28%,  $I^2 = 92.54%$ ,  $p < 0.001$ ), respectively.

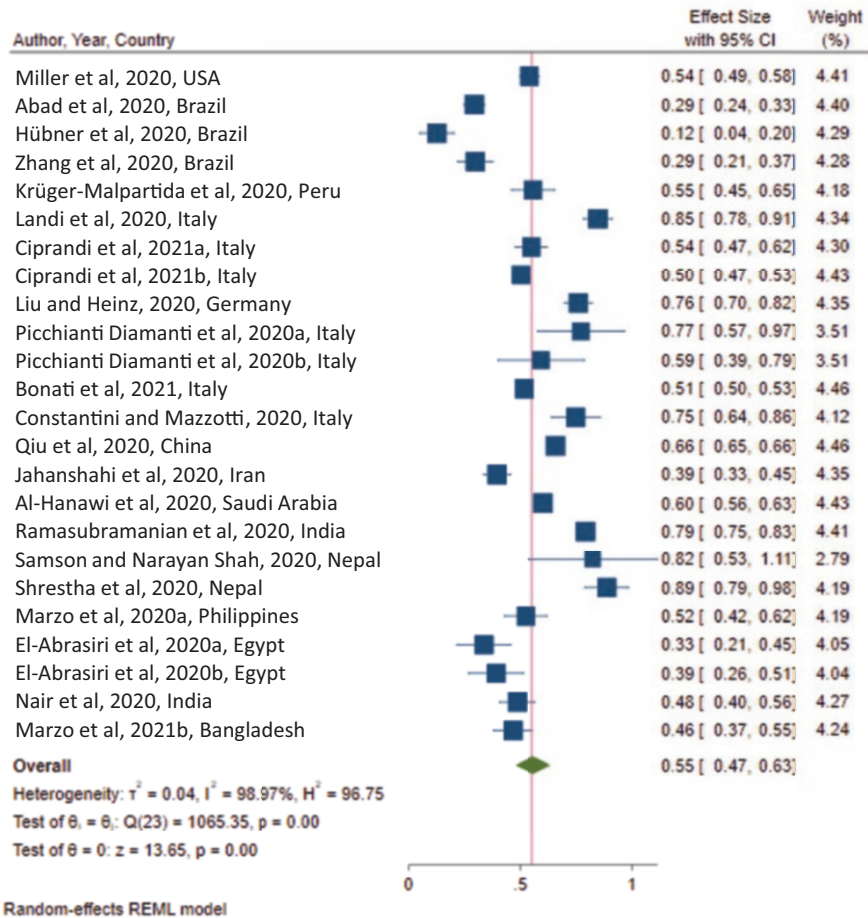
**Table 4.1** Characteristics of the included studies (a and b indicate different aspects of the same study)

First Author (Ref)	Country	Continent	Population	Size	Age (mean)	Female (%)	Prevalence of psychology distress based on CPDI tool (%)			
							Normal	Mild-to-moderate	Severe	
Miller et al. [22]	USA	Americas	Child welfare workers	1996	41.4	90.4	53.6	40.5	5.9	Good
Abad et al. [23]	Brazil	Americas	General population	1844	36.2	79.8	28.7	47.5	23.8	Good
Hübner et al. [24]	Brazil	Americas	Student	654	NA	76.6	12.08	52.9	35.02	Good
Zhang et al. [25]	Brazil	Americas	General population	638	NA	57.7	29.15	52	18.8	Good
Krüger-Malpartida et al. [26]	Peru	Americas	General population	400	41.0	65.5	55.3	35.5	9.3	Good
Landi et al. [30]	Italy	Europe	General population	944	38.8	73.5	84.5	10.3	5.2	Good
Ciprandi et al. (a) [31]	Italy	Europe	Adults with cystic fibrosis	712	NA	59.3	54.5	40.2	5.3	Good
Ciprandi et al. (b) [31]	Italy	Europe	General population	3560	NA	59.3	49.9	43.9	6.2	Good
Liu and Heinzl [13]	Germany	Europe	General population	1007	42.0	74.4	75.9	20.6	3.6	Good
Diamanti et al. (a) [27]	Italy	Europe	General population	100	50.5	59.0	77	22	1	Good
Diamanti et al. (b) [27]	Italy	Europe	Adults with autoimmune arthritis	100	57.7	72.0	59	38	3	Good
Bonati et al. [28]	Italy	Europe	General population	20,518	NA	69.9	51.4	43.4	5.3	Good
Constantini and Mazzotti [32]	Italy	Europe	General population	328	46.5	58.2	74.7	20.4	4.88	Medium
Qiu et al. [10]	China	Asia	General population	52,730	NA	64.7	65.6	29.29	5.14	Good
Jahanshahi et al. [35]	Iran	Asia	General population	1058	NA	53.8	38.9	47	14.1	Good
Al-Hanawi et al. [11]	Saudi Arabia	Asia	General population & healthcare workers	3036	NA	49.9	59.9	39.2	7.2	Good
Ramasubramanian et al. [12]	India	Asia	General population	2317	NA	64.2	78.98	20.63	2.72	Good



Samson and Narayan Shah [37]	Nepal	Asia	General population	45	NA	37.7	82.22	17.82	0	Medium
Shrestha et al. [34]	Nepal	Asia	General population	410	34.8	35.1	88.5	11	0.5	Good
Marzo et al. [38]	Philippines	Asia	General population	407	32.0	56.8	52.1	39.5	8.4	Good
El-Abasiri et al. (a) [39]	Egypt	Asia	Healthcare workers	266	NA	40.2	33.1	51.9	15	Good
El-Abasiri et al. (b) [39]	Egypt	Asia	General population	257	NA	69.6	38.5	39.7	21.8	Good
Nair et al. [36]	India	Asia	Endodontists	586	NA	46.9	48.12	38.23	13.65	Good
Marzo et al. [33]	Bangladesh	Asia	General population	501	NA	65.6	46.11	44.3	9.5	Medium

NA Not available; All studies were cross-sectional



**Fig. 4.2** Forest plot of CPDI-based pooled prevalence for normal psychological distress (note that years followed by a and b indicate different aspects of the same study). USA United States of America

For the European continent, the same pooled prevalence percentages of psychological distress across 8 studies (sample size = 27,269) were 65% (55.4–75.4%,  $I^2 = 96.67\%$ ,  $p < 0.001$ ), 30% (20.5–39.7%,  $I^2 = 96.38\%$ ,  $p < 0.001$ ), and 5% (4.1–6.5%,  $I^2 = 10\%$ ,  $p < 0.001$ ), respectively. For the 11 studies from the Asian continent (sample size = 61,613), the normal, mild-to-moderate, and severe pooled prevalence percentages of psychological distress were 57% (46–67.8%,  $I^2 = 98.07\%$ ,  $p < 0.001$ ), 34.6% (27.1–41.7%,  $I^2 = 95.42\%$ ,  $p < 0.001$ ), and 8.4% (5.1–11.8%,  $I^2 = 72.61\%$ ,  $p < 0.001$ ), respectively. Heterogeneity tests ( $I^2$ ) indicated low heterogeneity in the prevalence of severe psychological distress in European countries. However, significant heterogeneity existed across the prevalence of all levels of psychological distress for Asia and the Americas as described above.

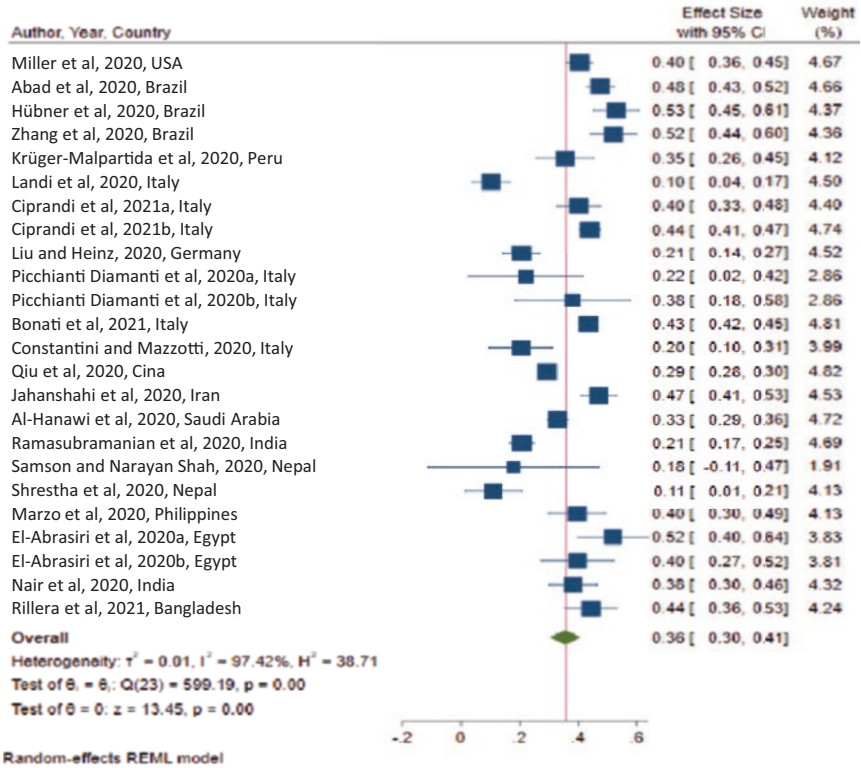


Fig. 4.3 Forest plot of CPDI-based pooled prevalence for (a) mild-to-moderate psychological distress and (b) severe psychological distress

### 3.5 Pooled Prevalence of Psychological Distress According to Gender

Prevalence data of CPDI-based psychological distress according to gender was available in seven studies (Table 4.2). The pooled prevalence of normal, mild-to-moderate, and severe psychological distress for females were 48% (34–63%,  $I^2 = 97.52\%, p < 0.001$ ), 40% (31–48%,  $I^2 = 91.17\%, p < 0.001$ ), and 13% (6–20%,  $I^2 = 88.29\%, p < 0.001$ ), respectively. The pooled prevalence of normal, mild-to-moderate, and severe psychological distress for males were 59% (47–71%,  $I^2 = 94.17\%, p < 0.001$ ), 34% (25–43%,  $I^2 = 90.22\%, p < 0.001$ ), and 5% (2–9%,  $I^2 = 26.36\%, p = 0.38$ ), respectively. A forest plot of the CPDI-based pooled prevalence for normal psychological distress in males and females is presented in Fig. 4.4 and for mild-to-moderate and severe psychological distress in Fig. 4.5a, b.  $I^2$  tests indicated low heterogeneity in the prevalence of severe psychological distress among males and in the separate male and female analyses. However, the  $I^2$  test indicated significant heterogeneity among the prevalence of psychological distress

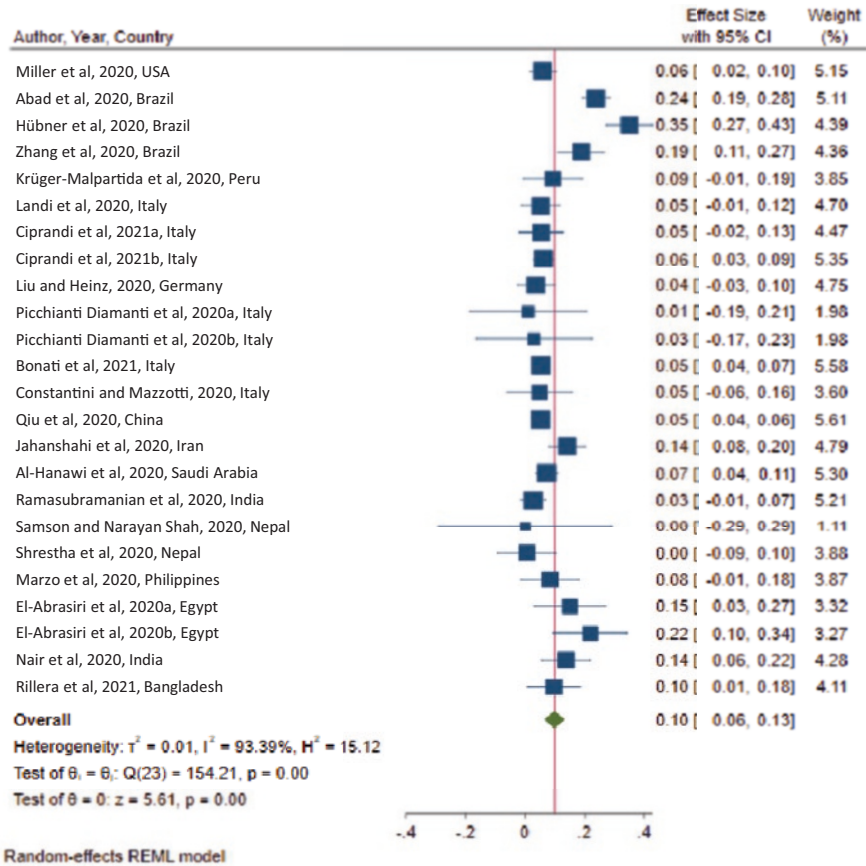


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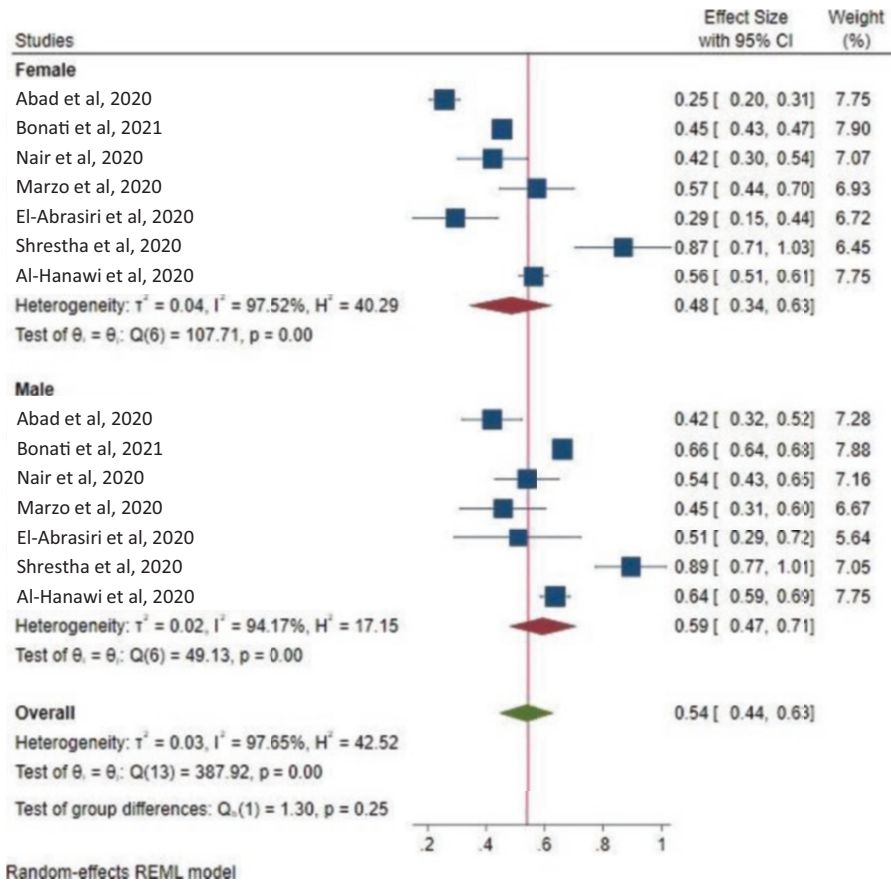
for females. Overall, the pooled prevalence of psychological distress was significantly higher in females than males (53% versus 39%  $p < 0.001$ ).

### 3.6 Publication Bias

Egger’s and Begg’s tests were used to assess publication bias. As indicated by the  $p$ -values for the pooled prevalence of normal CPDI-based psychological distress (Egger:  $p = 0.369$ , Begg:  $p = 0.551$ ) (Fig. 4.6a), mild-to-moderate psychological distress (Egger:  $p = 0.439$ , Begg:  $p = 0.785$ ) (Fig. 4.6b), and severe psychological distress (Egger:  $p = 0.995$ , Begg:  $p = 0.655$ ) (Fig. 4.6c), the funnel plots showed asymmetry and visual inspection confirmed the presence of publication bias.

**Table 4.2** Prevalence of CPDI-based psychological distress by gender

Author	Country	Continent	Sample size	Prevalence of psychology distress based on CPDI for female (%)			Prevalence of psychology distress based on CPDI for male (%)		
				Normal	Mild-to-moderate	Severe	Normal	Mild-to-moderate	Severe
Abad et al. [23]	Brazil	America	1844	25.5	47.3	27.2	41.6	48.4	10
Bonati et al. [28]	Italy	Europe	20,518	45.02	48.51	6.46	65.95	31.54	2.5
Nair et al. [36]	India	Asia	586	41.81	41.81	16.36	53.69	35.05	11.25
Marzo et al. [38]	Philippines	Asia	407	57.2	33.3	9.5	45.5	47.7	6.8
El-Abasiri et al. [39]	Egypt	Asia	523	29.4	48.9	21.7	50.3	39	10.7
Shrestha et al. [34]	Nepal	Asia	410	86.8	12.5	0.7	89.4	10.2	0.4
Al-Hanawi et al. [11]	Saudi Arabia	Asia	3036	56.2	36.2	8.3	63.6	29.6	6.7



**Fig. 4.4** Forest plot of CPDI-based pooled prevalence among females and males for normal psychological distress

## 4 Discussion

To our knowledge, this is the first study to report the prevalence of CPDI-based psychological distress impact of the COVID-19 pandemic in various countries, across the continents of the Americas, Europe, and Asia. We incorporated Middle East countries into the Asian continent as this region is officially classified as part of southwestern Asia [40]. We also included Egypt into the Asian continent as it officially recognized as part of the Middle East [41]. The analysis showed that the prevalence of the psychological distress in the mild-to-moderate and severe levels during the COVID-19 pandemic from January 2020 to January 2021 was highest for the Americas, followed by Asia and then Europe. In addition, the psychological distress in the mild-to-moderate and severe categories over this period was higher

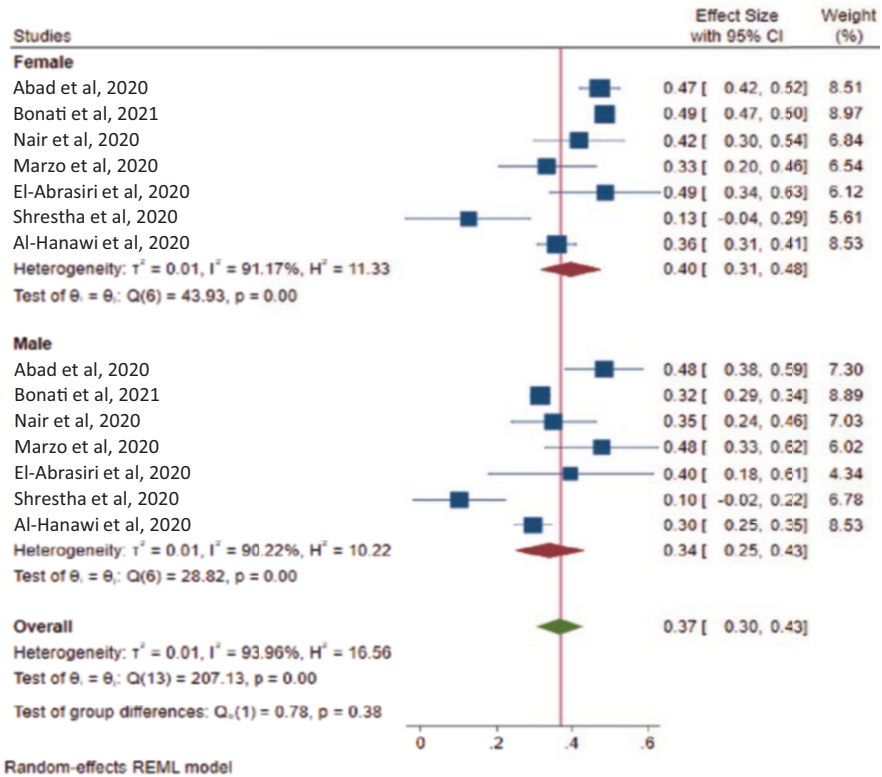


Fig. 4.5 Forest plot of CPDI-based pooled prevalence in females and males for (a) mild-to-moderate psychological distress and (b) severe psychological distress

for females compared to males. However, it should be noted that this finding was not analyzed across the separate continents.

The finding of greater psychological stress in females is consistent with the fact that women are generally more susceptible to depression and more likely to experience posttraumatic stress symptoms over time compared to males [42, 43]. In line with previous studies from Brazil [23] and Italy [28], women appear to show more psychological symptoms during quarantine in pandemics as compared to men. In this difficult situation, women can be faced with additional responsibilities, such as an increased role in family care, child support and teaching responsibilities due to school closures, as well existing gender inequalities and the potential for abuse from their partners [44]. In addition, the loss of daily routines, as well as social and physical contact with friends and family, can lead to isolation, boredom, or frustration [11, 34, 36, 38]. Moreover, previous studies have shown that fear of COVID-19 infection from family members and obsessive-compulsive disorders is higher in women [45, 46]. Taken together, these findings indicate that more careful attention



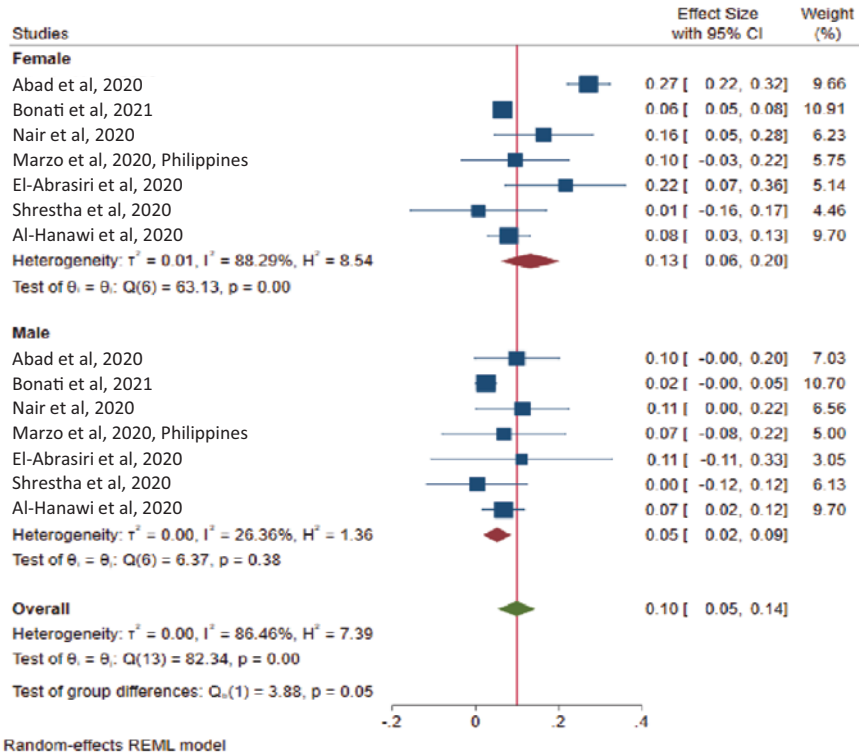


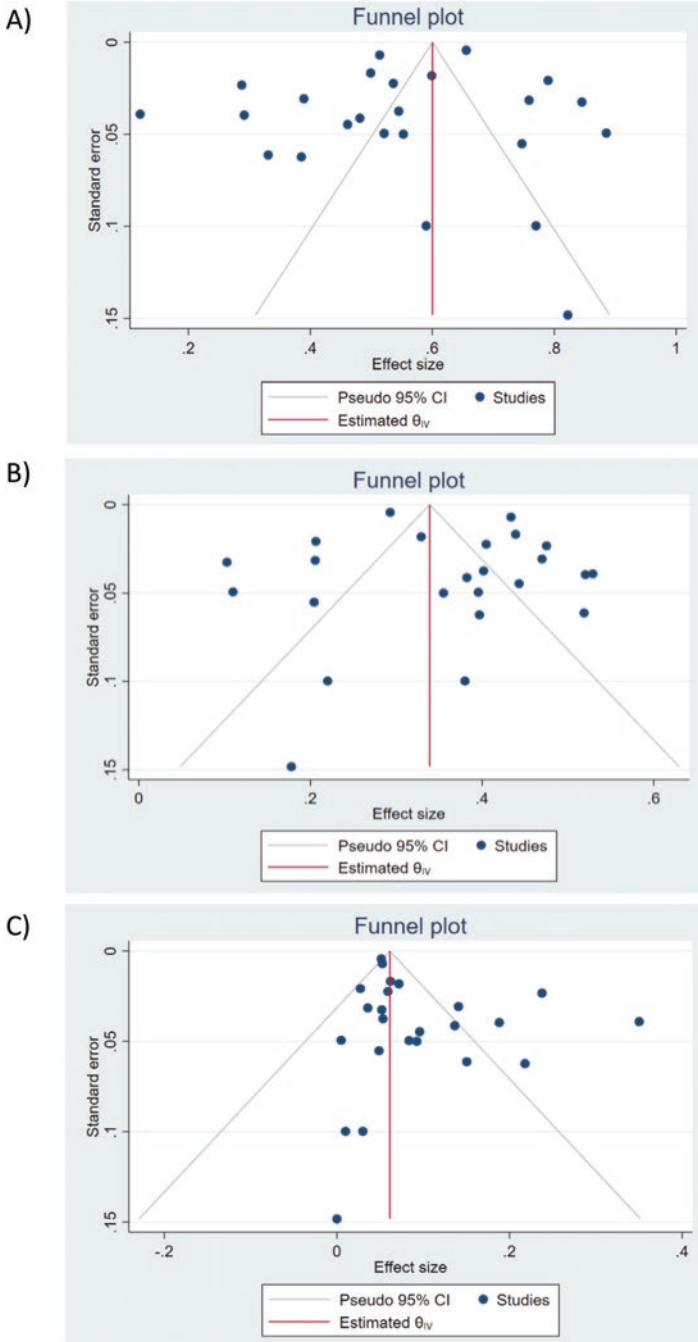
Fig. 4.5 (continued)

to risk identification and early intervention policies should be adopted for females during pandemics and other crises.

We found that the highest prevalence of psychological distress during the time of the COVID-19 lockdowns was highest in Brazil at 87.9% and lowest in Nepal (11.5%) for the combined mild-to-moderate and severe categories [24, 34]. The main difference in the prevalence of psychological distress between Brazil and Nepal is likely to be related to the more than 8.5 million persons in Brazil who had been infected by COVID-19 as of January 22, 2021 [2]. However, only 267 thousand cases of COVID-19 had been confirmed in Nepal over this same time period [2]. It is perhaps not surprising that the evidence shows a higher risk of mental distress in communities and countries with a higher prevalence of the disease [47], and this can also be related to the ensuing prolonged periods of quarantine and lockdown [3].

The finding that the pandemic-related psychological distress in the Americas was a larger problem than in Asia and Europe has not been reported previously. This is most likely driven by the high number of cases in both Brazil in South America and the USA in North America. In fact, the USA recorded the highest number of infections by January 22, 2021, at over 24 million cases [2]. Although COVID-19





**Fig. 4.6** Funnel plot showing publication bias on CPDI-based prevalence of psychological distress ranked as (a) normal, (b) mild-to-moderate, and (c) severe

infections were higher in Europe compared with Asia, a comparison of the two continents showed that the prevalence of psychological distress was significantly higher in Middle-East and Asian countries. Overall, this difference may be due to the higher testing rate in Europe and the potentially associated higher sense of security in the infected population. Moreover, European countries such as Germany and Italy had a lower COVID-19 case-fatality rate compared to China or Iran [2]. The results of previous studies on automobile accidents have suggest that self-reported fear is positively associated with mortality rate and differs across countries [48]. Other potential factors that may account for the observed variation in prevalence of COVID-19-related psychological distress across countries and continents include differences in restrictive measures, economic recessions, healthcare systems, biological, immunological, socio-demographics, and cultural differences [49–51].

There are some limitations to this study that should be considered in the interpretation of the data. First, all of the research in this meta-analysis were cross-sectional as they only gave a snapshot of the current situation with no longitudinal exploration. Second, there was lack of representation of studies in European countries other than Italy and Germany. Therefore, countries such as the UK where COVID-19 cases had reached over 3.5 million by the end of January, 2021 [2], were not represented. Third, it was not possible to assess gender differences between continents due to lack of data. For the same reasons, it was not possible to assess the prevalence of psychological distress for healthcare professionals compared to the general population. This is particularly important as many of these were on the front line exposed to high levels of physical and mental stress and had to cope with high levels of uncertainty, fear of contamination, and perceived lack of support [52–55]. Finally, the data provided by the studies included in this meta-analysis depended on the self-reported symptoms and signs via online survey. Thus, there is uncertainty related to actual mental status.

In future studies, the subjective nature of the online survey approach to assess psychological distress found be supported by more objective biomarker-based approaches. For example, the P1vital® PReDicT Test developed in Oxford, UK, provides an objective means of assessing a patient's mental state through a 15 min online test comprised of facial expression recognition tasks and a series of health-related questions [56]. The facial recognition aspect of the test works as people with a mental illness such as depression often show a negative bias by interpreting indistinct expressions as less happy compared to non-depressed controls [57]. In addition, there is now considerable evidence for the utility of easily accessible molecular biomarkers in assessing the mental state. For example, evening levels of salivary cortisol have been linked with anxiety, depression, and posttraumatic stress disorder [58]. The cortisol awakening response (CAR) which measures the increase in cortisol secretion 30 to 45 min after awakening has been used as a marker of hypothalamic-pituitary-adrenal (HPA) axis activation, which can occur in both physical and mental health conditions including psychological stress [59–61]. In these studies, cortisol can be measured by enzyme-linked immunoadsorbent assay (ELISA) [62]. In addition, salivary amylase enzymatic activity has been used to monitor the effects on workers in stressful or isolated environments [63]. There has been considerable

interest in the application of blood-based biomarkers such as cytokines, hormones, and growth factors in the study of mental disorders, which can be measured simultaneously using multiplex immunoassay platforms [64–66]. As examples, increased levels of C-reactive protein (CRP) and pro-inflammatory cytokines have been associated with depression following stroke [67], interleukins (IL)-1 $\beta$ , IL-5, and IL-6 have been detected in people with panic disorder [68], and the levels of brain-derived neurotrophic factor (BDNF) have been correlated with the disease progression of schizophrenia and depressive disorders [69]. Perhaps most critically, two studies also demonstrated the concept that mental illnesses could be detected several months or years before full manifestation with development of blood-based molecular biomarker algorithms for detection of individuals with a high risk of developing psychosis [70, 71]. In addition to assessing risk and current condition, all of the above digital and multiplex immunoassay approaches could be used to monitor any upsurge or recovery in mental status.

## 5 Conclusions and Future Perspectives

This meta-analysis suggested a high psychological impact due to the COVID-19 pandemic in many countries, with the highest levels detected in the Americas followed by Asian and European countries. In general, the distribution of the diverse spatiotemporal parameters of the pandemic may explain the heterogeneity in the degree of psychological distress among different geographical regions and countries. In addition, females appear to be more vulnerable to such distress and require further attention in terms of preventive and management strategies. However, the present study was limited by lack of a longitudinal analysis, poor representation of data from some countries in each continental group, and lack of data for assessment of gender differences on a per continent basis, and the reports of psychological stress levels were obtained by online survey and were therefore subjective in nature. Given these challenges, it will be important to incorporate the use of both digital and molecular biomarkers to increase the objectivity and accuracy of assessing the dynamic changes in mental health in the event of further disruptive waves of COVID-19 disease. There is also an urgent need for introduction of effective mental health interventions to assess and treat individuals in the highest risk groups for the best possible therapeutic outcomes.

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