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FROM COVID-19 TO PSYCHOLOGICAL DISTRESS: A SYSTEMATIC REVIEW ON QUARANTINE.

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ABSTRACT

Background. The novel coronavirus (SARS-COV-2) and related syndrome (COVID-19) has required a worldwide measure of quarantine with severe consequences for millions of people. Methods. Since psychopathological consequences related to social restrictions have been reported, a systematic review according to Cochrane Collaboration guidelines and the PRISMA Statement was performed to quantify the effects of quarantine on mental health of adults. Major databases - Pubmed, Scopus, Embase, PsycInfo, and Web of Science- were researched for observational studies with data on mental health indexes related to quarantine or isolation for epidemic infections. Results. Twenty-one independent studies were included for 82,312 subjects. Conclusions. The results showed that at least 20% of people exposed to these conditions reported a psychological distress, with a prevalence of PTSD, depression and, less often, generalized anxiety. Important methodological bias weakens the conclusion of most studies, opening to the need of further research on mental health after quarantine and related risk/buffering factors.

Key-words: Covid-19, psychological distress, anxiety, depression, PTSD

1. INTRODUCTION

On March 12, 2020, the World Health Organization (WHO) declared the 2019 novel coronavirus (SARS-COV-2) and related syndrome (COVID-19) outbreak a pandemic because almost 125,000 cases were reported to the WHO, from 118 countries and territories [1]. The adoption of restrictive measures in the perspective of public health is not new, with Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), Ebola, H1N1 influenza, and Equine Influenza that required quarantine in the past. However, this is the first outbreak of the modern age requiring a worldwide measure of quarantine to prevent the negative burden of the outbreak on people. It was progressively adopted measures of movement restrictions, closure of unnecessary activities and social isolation (quarantine) all over countries, with severe consequences in real life for millions of people. If the isolation of confirmed and suspected cases is a crucial part of these control efforts [2], the effect of quarantine on mental health is unclear. The warning on the psychopathological consequences of outbreak and related-quarantine during the recent COVID-19 has been delivered by several letters [2-6] and a qualitative review on previous outbreaks [7]. If the psychological burden of quarantine in terms of feelings of sadness, worries, loneliness or hypervigilance is part of the normal reactions of human beings to uncertain and hazardous situations, the shift towards overt psychopathologic disorders needs attention and studies. The comprehension of the consequences in term of mental health may help to guide future political choices, in order to balance the pros of limiting the pandemic and the cons of the burden on economic and psychological health. According to this aim, we present a

quantitative review of studies on the current (COVID-19) and previous outbreaks to analyse the consequences of quarantine in terms of mental health.

2. Materials and Methods

The objective of this systematic review is to analyse all observational studies realised on the burden of quarantine on mental health. The case-control study design, adequacy of sample size, comparison and outcome measures have been all carefully analysed to guarantee the right inclusion of selected studies.

Search strategy

Electronic searches were conducted on the major databases in the field of health and social sciences — Pubmed, Scopus, Embase, PsycInfo, and Web of Science — in order to include the broadest range of relevant literature. The search was performed using Mesh terms/Keywords (depending on the database) with the same search strategy: “Quarantine” AND “Pandemic” OR “Outbreak” OR “COVID-19” OR “Psychological distress” OR “Anxiety” OR “Depression” OR “Emotional distress/trigger” OR “Psychiatric disorder” OR “Post-Traumatic Stress Disorder (PTSD)” OR “Adjustment disorder”. The selection of the search terms is based on literature on mental health [8]. The search was limited to English-written publications, and to the period from 2000 to July 2020. The starting year was 2000 because we considered the last twenty years as adequate to cover a significant period where measure of quarantine were adopted consistently (we had outbreaks of Mers, Sars, Equine influenza, Ebola). The ending point of online search was July 2020 in order to include the growing evidence concerning mental health consequences of the current quarantine related to COVID-19 pandemic. It was also performed an additional analysis of

the reference list in each selected paper. The study was excluded if the full text was not retrievable.

This systematic review was based on the following inclusion criteria in order to consider studies of comparable quality, as well as to sustain the reliability and validity of results: a) studies should report data on mental health indexes linked to epidemic infections, which required containment interventions based on quarantine; b) studies should administer valid and reliable instruments, reporting the cut-off value of clinical relevance, to assess mental health impacts of quarantine; c) studies should be written in English.

Case reports, letters to the editor, meeting abstracts, book chapters were excluded in order to focus the attention on data collected during and after outbreaks and related containment interventions. Reviews were considered as additional sources of information for including empirical studies within the current systematic review. Furthermore, studies carried out on health care workers were excluded because this review aimed to evaluate mental health consequences of quarantine on general population, even though the topic has been object of a study by some Authors of the same group [9]. Ultimately, qualitative studies were excluded because the objective of this review was to attempt to quantify the impact of social isolation due to pandemic infection.

Data extraction

Study selection was performed by two independent reviewers with research expertise in clinical psychology (FG and RF) who assessed the relevance of the study for the objectives of this review. This first round of selection was based on the title, abstract,

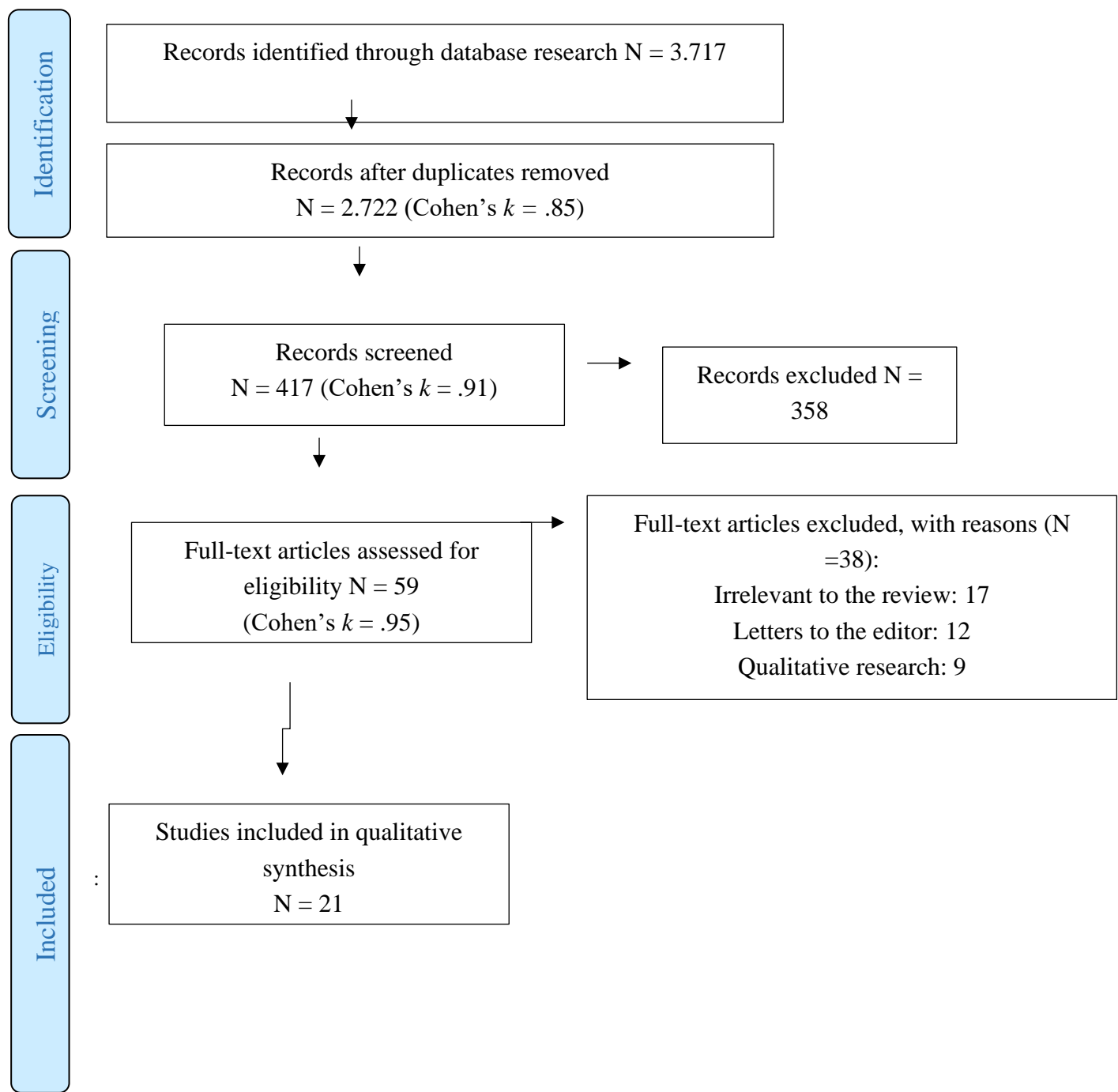
and keywords of each study. If the reviewers did not reach a consensus or the abstract did not contain sufficient information, the full text was reviewed.

In the second phase (screening), full-text reports have been evaluated to detect whether the studies met the inclusion criteria (Figure 1). In the phase of eligibility, all full texts were retrieved, and a final check was made to exclude papers not responding to inclusion/exclusion criteria, and reaching the final consensus to decide the final number of studies to be selected.

A standardised data extraction form was prepared; data was independently extracted by two of the authors (FG and MG) and inserted in an initial database ($N = 2.722$; Cohen's $k = .85$) [10]. From this initial database, FG and MG identified 417 studies (Cohen's $k = .91$) that reported at least one of keywords used for the current systematic review within the title and the abstract of each manuscript. Subsequently, FG and MG excluded papers ($N = 358$; Cohen's $k = .95$) that did not highlight a combination of keywords of this review linked "Quarantine" or "Pandemic" or "Outbreak" or "COVID-19" AND "Psychological distress" or "Anxiety" or "Depression" or "Emotional distress/trigger" or "Psychiatric disorder" or "Post-Traumatic Stress Disorder (PTSD)" or "Adjustment disorder". Fifty-nine studies were screened using inclusion and exclusion criteria previously discussed. FG and MG did not reach a consensus for the inclusion of 3 studies, especially considering the possibility to compute the percentage of sample reporting clinically significant levels of psychological distress. Therefore, a third reviewer (MC) resolved these discrepancies [11], carefully assessing method and result sections of each study in order to check whether it was

reported the cut-off value of instruments used to evaluate psychological distress and the portion of sample that surpassed this value.

Figure 1. PRISMA flow diagram of literature search and selection of publications.



Statistical methods

A systematic analysis was conducted according to the Cochrane Collaboration guidelines [11] and the PRISMA Statement [12]. Considering available data, it was not possible to conduct appropriate statistical analyses linked to a meta-analytic approach [13]. However, the current review provided a quantitative approach for aggregating results of studies, which considered as the main outcome the percentage of sample reporting clinically significant levels of psychological distress (for a description of cut-off scores see table 1). This index was primarily reported in the Results section of each study. With respect to overall psychological distress and each specific class of symptoms (i.e., PTSD; depression; anxiety), the analyses computed mean, standard deviation (SD), standard error (SE) and 95% confidence interval (CI) of the percentage of sample with clinically relevant scores. These indexes were estimated whenever at least three independent studies yielded data. Furthermore, in order to control possible confounding effects of sample size, year of publications on outcomes, Spearman's correlations (ρ) between them were performed. Furthermore, ρ was estimated between the length of quarantine period and outcomes, in order to provisionally test whether the effects of isolation on mental health depend on the period of exposure to this conditions, or alternatively, epidemic infections and related quarantine might considered themselves triggers for psychological suffering. The analyses also compared the percentage of clinically significant distress among specific symptoms using procedures based on the Z-test [13]. Bonferroni correction was applied when multiple comparisons were conducted. Moreover, Z-test procedures were used to evaluate whether other variables might affect the percentage of clinically significant psychological distress

(i.e., direct vs indirect exposure to isolation; retrospective assessment vs evaluations at the moment of epidemic infection and quarantine containment; Western culture vs Eastern culture).

Risk of bias

The current systematic review assessed quality of studies included using the rating scale developed by National Institutes of Health for observational cohort and cross-sectional research designs [14]. This scale is composed of 14 items rated on 3 levels (i.e. Yes; No; Not applicable [NA]). “No” rating indicates the presence of possible bias. “Yes” ratings reflect methodological strengths of research. The quality of each study was independently assessed by two authors (MC and FG), who reached a high inter-rater reliability (Cohen’s $k = .94$). At the end of the evaluation, ratings of each study were summed within each item of risk of bias scale in order to provide a quantitative approach to the assessment of quality of studies included in the current systematic review. Given the number of studies included in this review, the total score of risk of bias scale was 294. The percentage of each rating (i.e. Yes; No; NA) on total score was computed in order to show how methodological strengths and biases were distributed across studies

FINDINGS

Twenty-one independent studies [15-35] (Table 1) were included for a total of 82,312 subjects.

Table 1. Overview of the selected studies

Study	Sample description	Country	Disease	Study design	Quarantine length	Assessment tools	Outcome measure	% of clinical distress	Other significant findings	Note
Hawryluck et al., 2004 [15]	N = 129 Gender distribution non reported General population	Canada	SARS	Cross-sectional General population survey	Median 10 days	IES-R (cut-off ≥ 20) CES-D (cut-off ≥ 16)	PTSD symptoms Depressive symptoms	Overall 30.05% PTSD 28.9% Depression 31.2%	The duration of quarantine was significantly related to increased PTSD and depressive symptoms	Responders completed the survey at the end of quarantine and within the pandemic
Reynolds et al., 2008 [16]	N=1057 (37% M; mean age 49.2)	Canada	SARS	Cross-section General population survey	8 days	IES-R (cut-off ≥ 20)	PTSD symptoms	PTSD 14.6%	Health-care workers experienced more severe symptoms of PTSD ($p < .001$)	Responders completed the survey during quarantine and within pandemic
Taylor et al., 2008 [17]	N=2760 (15% M; mean age not reported)	Australia	Equine influenza	Cross-sectional Retrospective General population survey	Not reported	K10 (cut-off ≥ 30)	Anxiety and Depression	Anxiety and depression 14%	Individuals who lived high risk infection (red) zone were at much greater risk of high psychological distress. Younger people, and those with lower levels of formal educational qualifications were greater risk of high	Responders were quarantined during pandemic

									psychological distress	
Wang et al., 2011 [18]	N = 419 Quarantined N= 176 Nonquarantined N = 243	China	H1N1	Cross-sectional case-control studies	7 days	IES-R (cut-off ≥ 20) SRQ-20 (cut-off ≥ 7)	PTSD symptoms General mental health	Overall 1 12.9% Overall 1 PTSD 14.3% PTSD Quarantined 10.8% PTSD Not quarantined 16.87 % Overall 1 general mental health 11.45 % General 1 mental health quarantined 7.95% General 1 mental health	No significant differences for positive screening measures between quarantined and nonquarantined students	The survey was completed for all participants at the end of the quarantine period during the pandemic.

								Not quaran tined 14%		
Sprang & Silman, 2013 [19]	N= 398 (22% M; mean age = 37)	USA	H1N 1	Cross- sectional Retrospe ctive General populati on survey	Not reported	PCL-C parent (cut-off \geq 25) PTSD-RI Child (cut-off not reported)	PTSD symptoms	PTSD 25%	5.8% of parents scored above 30 on the PCL-C, indicating that the diagnostic threshold for PTSD was met. Children who experienced isolation or quarantine were more likely to meet the clinical cutoff score for PTSD (30%) than those who had not been in isolation or quarantine	Responders were quarantined during pandemic
Jeong et al., 2016 [20]	N=1692; N = 36 MERS cases (50% M; mean age = 52.3) N= 1656 isolated people (43% M; mean age = 43.9)	Kore a	MERS	Case- control (MERS cases vs isolated) Isolated people survey	21 days	STAXI (cut-off \geq 14) GAD-7 (cut-off \geq 10)	Anger Anxiety symptoms	Overall 1 9.02 Anger during isolation 17.4% Anger after isolation 6.9% Anxiety	Patients with MERS had significant high rates of clinical anger and anxious during the isolation period: MERS _{anger} = 52.8% (95% CI: 36.5 - 69.1%) Isolated _{anger} = 16.6% (95% CI: 14.8 -18.4%)	Responders were assessed during the isolation period and four to six months after removal from isolation.

								<p>during isolation n 8.4%</p> <p>Anxiety after isolation n 3.4%</p>	<p>MERS anxiety = 47.2% (95% CI: 30.9 - 63.5%)</p> <p>Isolated anxiety = 7.6% (95% CI: 6.3 - 8.9%)</p> <p>These differences were replicated after removal from isolation</p> <p>MERS anger = 30.6% (95% CI: 15.6 - 45.7%)</p> <p>Isolated anger = 6.4% (95% CI: 5.2 - 7.6%)</p> <p>MERS anxiety = 19.4% (95% CI: 6.5 - 32.3%)</p> <p>Isolated anxiety = 3.0% (95% CI: 2.2 - 3.9%)</p>	
Jalloh et al., 2018 [21]	N = 3564 (50% M; median age = 35)	Sierra Leone	Ebola	Cross-sectional Retrospective General population survey	21 days	<p>IES-6 (cut-off \geq 1.09 mean item equivalent to 24 on IES-R)</p> <p>PHQ-4 (cut-off \geq 6)</p>	<p>PTSD symptoms</p> <p>Depressive and anxious symptoms</p>	<p>Overall 11%</p> <p>PTSD 16%</p> <p>Depression 6%</p>	<p>Those participants who knew someone quarantined due to Ebola exposure alone were more likely to report symptoms of anxiety and depression (OR = 2.3;</p>	Responders were not directly quarantined

									<p>95%CI: 1.7-2.9, $p < .001$) and PTSD (OR = 2.0; 95%CI: 1.5 - 2.8, $p < .001$)</p> <p>Respondents who had both experiences (that is, they knew at least one person who died from Ebola and someone quarantined) were also more likely to report symptoms of anxiety and depression (OR = 1.8; 95%CI: 1.5 - 2.2, $p < .001$) and PTSD (OR = 2.3 95%CI 1.8 - 2.8; $p < .001$)</p>	
Kim et al., 2018 [22]	$N=27$ (37% M; mean age = 41.15)	Korea	MERS	<p>Cross-sectional</p> <p>Assessment of hospitalized individuals with confirmed ($N=18$) and suspected ($N=9$) MERS</p>	Not reported	<p>IES-R (cut-off not reported)</p> <p>KNHANE S-short form (cut-off not reported)</p> <p>PHQ-9 (cut-off ≥ 10)</p>	<p>PTSD symptoms</p> <p>Levels of stress</p> <p>Depressive symptoms</p>	<p>PTSD Not reported</p> <p>Levels of stress Not reported</p> <p>Depressive symptoms 40.7%</p>	<p>Confirmed Mers:17 (70.8%) exhibited psychiatric symptoms and 10 (41.7%) received a psychiatric diagnosis.</p> <p>Suspected MERS did not exhibit psychiatric symptoms</p>	<p>Participants were assessed during MERS pandemic (3 months) and therapeutic isolation</p>

Lee et al., 2018 [23]	N= 432 N= 359 hospital workers (18.1% M; mean age not reported) N=73 hemodialy sis patients (56.2% M; mean age = 61.3 (Sars, South Korea)	Kore a	SAR S	Cross- sectional Hospital workers survey and clinical assessme nt procedur es of patients with SARS	Not reported	IES-R Hospital workers (cut-off \geq 25) MINI Inpatients Depression (cut-off \geq 5) Anxiety (cut-off \geq 3) HADS Inpatients Depression (cut-off \geq 8) Anxiety (cut-off \geq 8)	PTSD symptoms Depressive symptoms Anxiety symptoms	Overall 1 25.6% PTSD Hospit al worker s 51.5% Depres sive sympto ms inpatie nts 10.3% Anxiet y sympto ms inpatie nts 11%	The healthcare workers who performed MERS-related tasks had significantly higher total IES-R scores (t =3.89, $p < .001$) and sub-scores, including hyperarousal (t = 3.535, $p <$.001), avoidance (t = 3.573, $p <$.001), intrusion (t = 3.756, $p <$.001), and sleep and numbness (t = 3.583, $p < .001$)	The initial sample of hospital workers were not quarantined. A second survey assessed PTSD symptoms among hospital workers (N=77; quarantined N = 23; not quarantined N = 54). However, the study did not report the % of sample which exceeded the IES- R cut-off score
Lei et al., 2020 [24]	N=1593 (38.7% M)	Chin a	COV ID- 19	Cross- section study	30 days	SAS (cut-off \geq 50) SDS (cut-off \geq .50)	Depressive symptoms Anxiety symptoms	Depres sion 7.3% Anxiet y 4.5%	Anxiety in affected was predicted by average household income (p = 0.028), self- perceived health condition ($p < 0.001$), property damage (p = 0.003); in unaffected	The study assessed several psychosocial risk for the onset psychiatric symptoms linked to quarantine. No subgroup analyses were conducted considering different levels of exposure to illness

									group by divorced/widowed ($p = 0.001$), self-evaluated level of knowledge ($p = 0.032$) and self-perceived health ($p = 0.001$). Depression in affected group predicted by education level ($p = 0.015$), self-perceived health condition ($p < 0.001$), property damage ($p = 0.002$); in unaffected group by divorced/widowed ($p < 0.001$), self-perceived health condition ($p < 0.001$), being worried about being infected ($p = 0.006$) and presence of psychological support ($p = 0.043$).	
Li et al., 2020 [25]	$N = 5033$ (33.3% M)	China	COVID-19	Cross-sectional General population survey	Not reported	GAD-7 (cut-off ≥ 8) PHQ-9	Anxiety Depression	Anxiety 20.4% Depression	Anxiety and/or depression was significantly associated with time spent on COVID-19	The study evaluated different content of anxiety and depression symptoms linked

						(cut-off ≥ 8)		20.4%	<p>related news per day (p<0.001). Anxiety was associated with psychological stressors like “I worry about myself and my loved ones being infected by COVID-19” (OR=1.95, 95% CI: 1.54-2.49), “I worry about my income, job, study or ability to pay the loan being affected” (OR=1.38, 95% CI: 1.13- 1.68), and “Home quarantine causes great inconvenience to my daily life” (OR=1.31, 95% CI: 1.04-1.64). The same psychological stressors were associate with depression (respectively OR=1.24, 95% CI: 1.04-1.50; OR=1.58, 95% CI: 1.35-1.86; OR=1.42, 95% CI: 1.18- 1.70)</p>	<p>to consequences of specific stressors. The absence of longitudinal data did not allow to assessed the temporal stability of risk factors for the development of psychiatric symptoms</p>
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Liu et al., 2020 [26]	N = 217 (41.5% M; mean age 21.7)	China	COVID-19	Cross-sectional student population survey	30 days	GAD-7 (cut-off \geq 8) PHQ-9 (cut-off \geq 8)	Depression Anxiety	Depression 35.5% Anxiety 22.1%	Prevalence of depression and anxiety were not significantly different in students according to gender ($p = 0.155$), Geographical location ($p = 0.356$) and grade ($p = 0.097$).	The study assessed high risk population for developing psychiatric conditions as a consequence of quarantine. The number of participants of study was small for generalizing results to other student population
Mazza et al., 2020 [27]	N= 2766 (28.3% M; mean age 32.94)	Italy	COVID-19	Cross-sectional General population survey	14 days	DASS-21 depression (cut-off \geq 21) DASS-21 anxiety (cut-off \geq 15) DASS-21 stress (cut-off \geq 27)	Depression symptoms Anxiety symptoms Stress symptoms	Depression 32.8% Anxiety 19.0% Stress 29.2%	Stress was associated with female gender ($p < 0.001$), negative affect, ($p < 0.001$), detachment ($p < 0.001$), acquaintance infected ($p < 0.001$). Depression with female gender ($p < 0.001$), negative affect ($p < 0.001$), detachment ($p < 0.001$), having an acquaintance infected ($p < 0.001$) history of stressful situations ($p = 0.008$), medical	This longitudinal study evaluated the impact of personality as a relevant risk factor for the onset of psychiatric symptoms. The study also included the assessment of different levels of exposure to illness

									problems (p=.047). Anxiety was associated with female gender (p<0.001), negative affect (p<0.001), detachment (p<0.001), history of stressful situations (p = 0.008), medical problems (p = 0.001), and a family member infected (p<0.001).	
Moccia et al., 2020 [28]	N = 500 (40.4% M)	Italy	COVID-19	Cross-sectional General population survey	30 days	K10 (cut-off ≥ 19)	Anxiety and Depression	Anxiety and depression 18.6%	Cyclothymic (p < 0.001), depressive (0.001), anxious temperament (p = 0.002) and sub-item “Need for Approval” (p = 0.01) were risk factors for moderate-to-severe psychological distress; sub-item “Confidence” (p = 0.002) and sub-item “Discomfort with closeness” (p = 0.001) of Attachment	The study showed that interpersonal styles were risk and protective factors for the development of psychiatric symptoms. The online survey lasted only four days.

									Style Questionnaire were protective factors.	
Odriozola-González et al., 2020 [29]	N= 2530 (33.9% M)	Spain	COVID-19	Cross-sectional University survey	10 days	DASS-21 (cut-off: not reported) IES (cut-off ≥ 26)	Depression Anxiety Stress PTSD symptoms	Depression 34.19 % Anxiety 21.34 % Stress 28.14 % PTSD symptoms 12.5%	Students from Arts & Humanities and Social Sciences & Law showed higher scores related to anxiety, depression, stress and impact of event with respect to students from Engineering & Architecture. University staff presented lower scores in all measures compared to students, who seem to have suffered an important psychological impact during the first weeks of the COVID-19 lockdown.	The study compared the psychological impact of outbreak between students from different departments and staff of university. The study did not include the evaluation specific factors that could explain the difference in levels of severity of psychiatric symptoms among these group
Ozamiz-Etxebarria et al., 2020 [30]	N = 976 (18.9% M)	Spain	COVID-19	Cross-sectional General population survey	Not reported	DASS-21 (cut-off: not reported)	Depression/Anxiety Stress	Depression 22.0% Anxiety 28.8% Stress 22.0%	Younger individuals with chronic diseases reported more symptoms than the rest of the population. The	The study did not consider psychosocial risk factors that were involved in explaining severity of psychiatric symptoms.

									study also detected higher levels of symptoms after the stay-at-home order was issued. Such symptoms are predicted to increase as the confinement continues.	The study recruited participant from a specific region of Spain
Qiu et al., 2020 [31]	N = 52730 (35.2% M)	China	COVID-19	Cross-section General population survey	21 days	CPDI (cut-off \geq 52)	Anxiety and depression symptoms, together with related behaviors	Anxiety and Depression 35%	Female respondents showed significantly higher psychological distress than their male counterparts ($p < .001$). Individuals between 18 and 30 years of age or above 60 presented the highest CPDI scores	Responders completed the survey during the quarantine
Somma et al., 2020 [32]	N= 1043 (18.5% M)	Italy	COVID-19	Cross-section General population survey	10 days	SDQ EPS (cut-off \geq 7)	Emotional and behavioral problems	Overall 13.2%	Negative affectivity ($t(1041) = 19.02$, Cohen's $d = 1.18$) and detachment ($t(1041)=13.32$, Cohen's $d = 0.83$) represented relevant risk factors for reduced	The study showed that maladaptive personality traits were involved in explaining the onset of psychological distress during quarantine. The characteristics of sample did not allow to

									emotional well-being	generalize results to Italian population
Tang et al., 2020 [33]	N=2485 (39.2% M)	China	COVID-19	Cross-sectional Students population survey	30 days	PCL-C (cut-off ≥ 38) PHQ-9 (cut-off ≥ 10)	PTSD symptoms Depressive symptoms	PTSD 2.7% Depression 9.0%	Feeling extreme fear was the most significant predictor for both depression (, p<0.001) and PTSD (p<0.001), followed by short sleep duration (p<0.001), living in the worst-hit areas (p<0.001); Sleep duration was observed to be a mediator between number of exposures and PTSD (z=0.104, 95% CI: 0.016, 0.204), or depression (z=.065, 95% CI: 0.010, 0.126)	The study showed a key role of neurovegetative alterations on the development of psychiatric symptoms during quarantine. The study recruited a sample composed of students. Therefore, this characteristics of sample did not allow to generalize results
Fawaz et al., 2020 [34]	N = 950 (69.3% M)	Lebanon	COVID-19	Longitudinal survey on general population	30 days	PCL-C (cut-off ≥ 3)	PTSD symptoms	37.72 %	No difference in the prevalence of PTSD symptoms among genders (p = .07), among	This study was carried out a pre-post-test research design. Furthermore, it was included the evaluation of different levels of

									occupations (health care worker or not, p = .34), age (p = .15) and leaving home during quarantine or not (p = .77), but the possible sources of exposure to COVID-19 (p = .02). Gender, age, occupation, potential sources of exposure and leaving home or not were not predictors of PTSD.	exposure to illness. However, the study did not consider relevant psychosocial risk factor for the development of psychiatric symptoms
Germani et al., 2020 [35]	N= 1011 emerging adults (28.7% M)	Italy	COVID-19	Cross-sectional General population survey		STAI-Y (cut-off ≥ 40) PSS (cut-off ≥ 14)	Anxiety Stress	Not reported	State anxiety (STAI-Y, mean ± SD: 48.56 ± 12.73) and stress levels (PSS, mean ± SD: 21.59 ± 7.16) were above the normal cut-off. Collectivistic orientation was related to higher perceived risks of infection (horizontal collectivism with general concern: coeff = 0.18; with	The study assessed the role of cultural and several psychosocial factors on the severity of psychiatric symptoms during quarantine. The convenience sampling method did not allow to generalize results

									personal concern: coeff = 0.12; with relatives/others concern: coeff = 0.13, all p<0.001; vertical collectivism with general concern: coeff = 0.20; with personal concern: coeff = 0.23; with relatives/others concern: coeff = 0.18, all p<0.001) and predicted lower psychological maladjustment, controlling for socio-demographic variables (horizontal collectivism: B = -0.24, -0.3 - -0.18 95% CI, p<0.001).	
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CES-D = Center for Epidemiologic Studies—Depression Scale; CPD = COVID-19 Peritraumatic Distress Index; GAD-7= Generalized Anxiety Disorder Scale; HADS = Hospital Anxiety and Depression Scale; IES-6: Impact of Event Scale-6; IES-R: Impact of Event Scale-Revised; K-10 = Kessler 10; KANES: Korean National Health and Nutrition Examination Survey; M= Men; MERS: Middle East Respiratory Syndrome; MINI = Mini International Neuropsychiatric Interview; PCL-C = PTSD Check List - Civilian Version; PHQ-4,9 = Patient Health Questionnaire-4,9; PSS: Perceived Stress Scale; PTSD= post-traumatic stress disorder; PTSD-RI = PTSD Check List - Civilian Version; SDQ-EPS = Strengths and Difficulties Questionnaire Emotional Problems scale; SRQ-20 = Self-Report Questionnaire STAXI = State-Trait Anger Expression Inventory

Table 1 provides a detailed description of the characteristics of each study [15-35]. First of all, up to 20% (95% CI: 14.47% – 27.21%) of individuals reported clinically significant levels of psychological distress in relation to direct and indirect exposures to epidemic infections and related quarantine containment interventions. The percentage of sample reporting high levels of distress was not related to year of publication ($\rho = .04$ [-.44 – .52]; $p = .92$; $N = 20$), sample size ($\rho = -.15$ [-.64 – .43]; $p = 0.18$; $N = 20$) and length of period of isolation ($\rho = .00$ [-.50 – .50]; $p = 1.00$; $N = 15$). Furthermore, retrospective studies (23.33% [10.21 – 36.44]) showed the same results of research carried out during epidemic infections (22.21% [14.44 – 29.96] ($Z = .07$; $p = 0.38$), as well as the analysis did not detect an effect of culture (Western: 23.42% [16.68% – 30.15%]; Eastern: 20.46% [9.15% – 31.76%]; $Z = .20$; $p = 0.39$).

Considering PTSD, the results highlighted that up to 21% (95% CI: 10.95% – 32.36%) of subjects reported clinically significant symptoms and, there were no differences between direct (15.75%; 95% CI: 6.29% – 25.20%) and indirect (33.75%; 95% CI: 10.83% – 56.66%) exposures to isolation conditions ($Z = .80$; $p = 0.29$). The percentage of sample reporting clinically significant PTSD was not related to year of publication ($\rho = -.11$ [-.77 – .63]; $p = 0.76$; $N = 10$), sample size ($\rho = -.39$ [-.83 – .33]; $p = 0.26$; $N = 10$) and length of period of isolation ($\rho = .62$ [-.45 – 1.00]; $p = 0.19$; $N = 6$).

Similar findings were extended to depressive symptoms. Specifically, studies found that 22.69% (95% CI: 13.04% – 32.33%) of participants highlighted clinically relevant symptoms of depression. The portion of sample reporting high levels of depressive symptoms was independent of year of publication ($\rho = .02$ [-.59 – .57]; $p = 0.95$; $N = 12$), sample size ($\rho = -$

.03 [-.76 – .80]; $p = 0.91$; $N = 12$) and length of quarantine ($\rho = -.33$ [-.97 – .95]; $p = 0.42$; $N = 6$).

The analysis revealed lower rates (16.16%; 95% CI: 8.20% – 24.12%) of clinically significant symptoms of anxiety, although they were not significantly different from PTSD ($Z = -.32$; $p = .38$) and depressive ($Z = -.43$; $p = 0.36$) symptoms. The percentage of clinically significant symptoms of PTSD was not statistically different from the depressive ones ($Z = -.05$; $p = 0.40$). With respect to the portion of sample reporting high levels of anxious symptoms, the year of publication ($\rho = .56$ [-.07 – .91]; $p = 0.07$; $N = 11$), sample size ($\rho = .30$ [-.38 – .80]; $p = 0.37$; $N = 11$) and length of period of isolation ($\rho = -.28$ [-1.00 – .65]; $p = 0.54$; $N = 7$) were not confounding variables.

Only two studies [28,35] analysed the existence of protective factors for a negative outcome: the Attachment Style Questionnaire showed that “Confidence” (OR: 0.92; $p = 0.039$) and “Discomfort with closeness” (OR: 0.94; $p = 0.023$) subscales were protective for higher psychological burden; horizontal collectivism (to see themselves as being similar to others and emphasizes common goals with others, interdependence, and sociability) is another factor linked to likely positive outcome ($p < 0.001$). The role of gender was analysed in few studies with female more at risk [26, 27, 31] than male, with one exception [34].

Risk of bias assessment (Table 2) showed a total score of overall strengths of studies included equal to 107 (36.3%). The facet reflecting overall biases highlighted a score of 111 (37.7%). Therefore, methodological strengths and biases were equally distributed across studies included in the current system review. The most recurrent weakness of studies referred to the

absence of multiple longitudinal assessments (21 studies) and the lack of adequate control of possible confounding factors on outcomes (20 studies).

Table 2. Assessment of risk of bias ($N = 21$)

Criteria	Yes	No	NA
1. Was the research question or objective in this paper clearly stated?	19	2	0
2. Was the study population clearly specified and defined?	17	4	0
3. Was the participation rate of eligible persons at least 50%?	8	6	7
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	20	1	0
5. Was a sample size justification, power description, or variance and effect estimates provided?	4	17	0
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	0	21	0
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	1	20	0
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	0	0	21
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	21	0	0
10. Was the exposure(s) assessed more than once over time?	0	0	21
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	14	6	1
12. Were the outcome assessors blinded to the exposure status of participants?	1	14	6
13. Was loss to follow-up after baseline 20% or less?	1	0	20
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	1	20	0
Total score	107	111	76

NA= Not Applicable

DISCUSSION

The current systematic review sought to investigate the impact of epidemic infections and related quarantine containment interventions on mental health and psychological distress [36]. Specifically, this study attempted to lay the foundations for an adequate response of mental health services. With this in mind, the current review aggregated results from prior studies that investigated such topic during similar epidemic infections, albeit significantly less widespread, together with provisional data collected during current COVID-19 outbreak. Overall, empirical findings suggested that at least one out of every five people reported a clinically significant psychological distress, independently of the length of isolation and culture. This finding is fully in line with other empirical studies which demonstrated that the isolation related to medical conditions significantly predicted the onset of psychological distress [37]. In addition to the adverse effects of isolation, the psychological distress linked to epidemic infections is largely in line with the well-recognized dysfunctional cognitive and emotional mechanisms underlying the fear of contamination [38]. With respect to the onset of specific symptoms, the analysis showed that the most recurrent clinical conditions associated to epidemic infections referred to PTSD and depression. Specifically, up to 20% of individuals who either directly or indirectly experienced an epidemic infection reported the onset of clinically significant symptoms of such conditions. Since January 2020 (date of declaration of Covid-19 in China), a sentiment analysis of Chinese social media showed an increase in negative emotions (anxiety and depression) and a decrease in life satisfaction [39]. Considering PTSD symptoms, this evidence might be related to fact that an epidemic infection represents a direct or indirect exposure to a threatened (potential) death, which is

considered the core diagnostic criterion for PTSD [8]. On the contrary, the high occurrence rates of clinically significant levels of depression might be linked to the well-established effects of social isolation and relational deprivation on emotional and cognitive functioning [40, 41]. The high occurrence of generalized anxiety symptoms, albeit less pronounced than the other conditions, might be associated to a heightened vigilance [42] and worry [43] towards threats related to diffusion trends of epidemic infections and their consequences on every-day life [44]. According to this evidence, it is plausible to expect that at the end of the current COVID-19 pandemic, one out of every five people might develop a clinically significant psychological distress. Particularly, the recurrent conditions might be PTSD, depression and (less) generalized anxiety.

Another side of interest is linked to the detection of risk or buffering factors for developing psychopathology. Focusing current research on the investigation of risk/buffering factors for consequences on mental health should be pivotal in order to address better psychological interventions. From the current review, some evidence arise towards a protective role for factors as secure or avoidant attachment style [28] and social openness (sharing common goals with others, interdependence, and sociability) [35]. On the other hand, female gender, negative affect, and detachment [27], dysfunctional personality traits or temperament (Negative affectivity, Detachment and Disinhibition) [28,32], severe property damage and low self-perceived health condition [24], younger age with/without chronic disease [17, 30] or feeling extreme fear [33] seem to be predictive of the worst outcome in terms of mental health. Current findings are consistent with the literature on traits

characteristics and mental health outcomes, which found that personality traits such as neuroticism, female gender, younger age and chronic disease are positively associated with poorer mental health outcomes [45-47]. Moreover, state variables such as fear of infection during pandemic are associated with elevated levels of psychological distress [7].

Looking at such symptomatology and the context of its development, mental health professionals should provide tailored assessment and interventions for distressing and post-traumatic reactions.

In the context of Covid-19, psychological assessment and monitoring should include queries about Covid-19– related stressors (such as exposures to infected sources, infected family members, loss of loved ones, and physical distancing), secondary psychological consequences (economic loss, depression, anxiety, psychosomatic preoccupations, sleep disorders, increased substance use, familial conflicts and/or domestic violence), and indicators of previous vulnerability conditions (such as preexisting physical or psychological conditions). Psychoeducation or cognitive behavioral techniques may be beneficial for some patients; others will benefit of formal mental health evaluation and care [48].

Despite this systemic review showed a clear scenario concerning psychological effects of epidemic infections and related quarantine containment interventions, it must be discussed some limitations. First, all studies were based on the administration of self-report measures that might produce a portion of false-positive cases. Therefore, the current findings should be confirmed using adequate structured clinical interviews (e.g. Structured clinical interview for DSM-5 disorders: Clinician version) [17]. Second, all studies included were cross-sectional naturalistic research designs. This did not allow to definitely concluding that the

event of epidemic infection and related quarantine interventions are the primary causes of the onset of psychological distress. Hence, empirical research should identify concurrent risk factors that facilitate the development and maintenance of these clinical conditions. The studies cover a range of different viruses/conditions and a range of participants, including those who had the condition, those who did not have the condition but family members who did and those who did not have the condition but were quarantined. It is possible that different types of exposures will produce very different types of psychological reactions and produce different rates of distress/psychopathology. Other factors (e.g., socioeconomic status, access to medical care, chronic disorders etc.) would also affect psychological distress and lead to different rates of psychological distress. Ultimately, the absence of multiple longitudinal assessments did not allow precisely evaluating the course of psychological distress after epidemic infections and quarantining containment procedures. Furthermore, the lack of evaluation of incidence rates of each psychological condition before the onset of epidemic infections limited to draw definitive conclusions concerning the extent of impact of such phenomena on development of psychological distress. At present, there are too few studies to examine these different critical issues and produce robust and replicable estimates of psychological distress. Of course, this historical period represents a matchless opportunity to study the clinical psychological burden of quarantine both for the long period length and for the worldwide diffusion of the social isolation. Last but not least, the wide use of survey with participation on voluntary basis add an important risk of bias. We need to study the psychological consequences of quarantine addressing the way people cope with social isolation, the predictors of maladaptive functioning, the role of pre-Covid-19 personality and

mental health issues. People after hospital admission for Covid-19 should have a special attention in order to test the burden in terms of PTSD, anxiety and/or depression.

Despite these limitations, this is the first quantitative systematic review that provisionally estimates the extent of psychological distress associated to past and current epidemic infections and related quarantine interventions. Results suggest that almost one out of every five people is at risk of development of clinically significant psychological distress during and after epidemic infections. Accordingly, mental health professionals should get ready to address a possible pandemic psychological suffering linked to the current COVID-19 pandemic infection.

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