Impact of the first Covid-19 pandemic wave on first episode psychosis in Milan, italy.

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A B S T R A C T

The ongoing Corona Virus Disease 2019 (COVID–19) pandemic appears to increase risk for mental illness, either directly due to inflammation caused by the virus or indirectly due to related psychosocial stress, resulting in the development of both anxious-depressive and psychotic symptoms. The purpose of the present study was to assess the frequency and characteristics of all patients with First Episodes Psychosis (FEP) without COVID-19 infection hospitalized in the first four months since lockdown in Milan.

We recruited sixty-two patients hospitalized between March 8 to July 8, 2020 versus those first hospitalized in the same period in 2019. The two subgroups were compared for sociodemographic variables and clinical characteristics of the episodes. Patients with FEP in 2020 were significantly older than patients with FEP in 2021, and presented with significantly less substances abuse.

Interestingly, patients presenting with FEP in 2020 were significantly older than patients with FEP in 2019. These data are compatible with the greater vulnerability to stressful factors during the pandemic, as well as with the greater concern regarding a possible COVID-19 infection producing brain damage causing the FEP.

1. Introduction

The ongoing Corona Virus Disease 2019 (COVID–19) pandemic, with more than 47 million confirmed cases worldwide at the time of writing, is having a substantial impact on the life of billions of people. Soon after the pandemic outbreak, several authors expressed their concern over the potential consequences of this crisis on global mental health, that is likely to substantially burden health systems (Torales et al., 2020; Fusar-Poli et al., 2020; Fiorillo and Gorwood, 2020). Systematic research is necessary to understand the extent of such phenomenon.

A systematic review recently suggested an increase in post-traumatic stress symptoms (PTSS) and depressive symptoms in patients with current or prior SARS-CoV-2 infection (Vindegaard and Eriksen Benros, 2020). Moreover, individuals already diagnosed with severe mental illness have been hypothesized to be at increased risk of infection and unfavorable outcomes (Druss, 2020; D'Agostino et al., 2021). Very limited data on the consequences of the pandemic on mental health in the general population is available at the current time. The adverse psychological effects caused by the social distancing, enforced or suggested by authorities in order to contain the spread of the viral infection, are a major cause of concern (Qiu et al., 2020). Several authors predicted an increase in incidence rates of depression, anxiety and PTSD in the general population (Brooks et al., 2020; Brown et al., 2020; Galea et al., 2020; Rogers et al., 2020; Salari et al., 2020). Moreover, worsening of psychiatric symptoms in subjects with preexisting psychiatric disorders and increased depressive symptoms, anxiety, psychological distress and sleep disturbances in health care workers have also been reported (Vindegaard and Eriksen Benros, 2020). Finally, evidence from MERS and SARS pandemics and the correlation of the pandemic with risk factors for suicide, such as the unemployment rate, suggest suicide rate

is also likely to increase worldwide (Chan et al., 2006; Barbisch et al., 2015; Brown et al., 2020; Kawhola et al., 2020; Sher, 2020; Sher, 2020). It is also worth noting that several cases of post viral exposure psychosis have been reported in the last year, reinforcing the hypothesis of the viral origin of schizophrenia (DeLisi, 2021).

Regarding the impact of the pandemic on psychosis, the available literature is currently limited. An increase in psychosis rates could be associated with viral exposure or steroid treatment, but also with pre-existing vulnerability and psychosocial stress (Radua et al., 2018; Brown et al., 2020). Notably, reports of stress–related psychotic episodes have begun to emerge worldwide in non-infected individuals (Elliot, 2020; Finatti et al., 2020; Shanbour et al., 2020; Zulkifli et al., 2020). We recently reported a case series of six patients with a negative psychiatric history, who were hospitalized due to psychotic episodes in one of Milan's University Hospitals during lockdown (D'Agostino et al., 2020). Milan is the largest city in Lombardy, which was globally described as the region with the worst impact of the pandemic in the early stages of the outbreak.

Most of the patients were above the typical age of onset for psychosis and presented with COVID–19–related somatic delusions. These episodes presumably reflect the intense psychosocial stress experienced during the pandemic, and the consequent neurobiological alterations that it entails (Heinz et al., 2019; Brown et al., 2020). In particular, dysregulation of dopaminergic signaling is often secondary to psychosocial stress, resulting in the phenomenon of aberrant salience (Mizrahi, 2016; Heinz et al., 2019). Whether this observation reflects an epidemiologically relevant phenomenon in the general population remains to be confirmed.

Therefore, we designed a study to (i) assess the frequency and characteristics of all First Episodes Psychosis (FEP) patients hospitalized in the first four months since lockdown in all three University Hospitals of Milan and (ii) make a comparison with data from the same timeframe in the previous year.

2. Methods

2.1. Patients

Individuals hospitalized on the inpatient units of three Departments of Mental Health located in Milan (Policlinico University Hospital, Sacco University Hospital, and San Paolo University Hospital) for a first episode psychosis between 8th March and 8th July 2020 and in the same period of 2019 were included in this study. These departments cover a catchment area corresponding to approximately half the 1.4 million population of Milan's inner city. We selected all admitted patients satisfying the following inclusion and exclusion criteria. The inclusion criteria were: 1) psychiatric hospitalization between 8th March and 8th July, 2020; 2) domicile in Lombardy at the time of admission. Exclusion criteria were: 1) previous psychiatric hospitalization; 2) evidence of lifetime psychotic symptoms; 3) diagnosis of dementia or other organic disorders potentially responsible for the psychotic symptoms. All participants enrolled in the study had signed an informed consent regarding the privacy of their data (epidemiological and clinical) and their treatment. As the sites of enrolment consist in university hospitals, a standard document is signed by the patients at the very admission into the psychiatric ward. At any time, the informed consent could be withdrawn by the patient.

The following socio-demographic variables were collected: age, gender, marital status, people in the household, job. In addition, we collected the following clinical variables: substance abuse, duration of illness, date of beginning and end of hospitalization, hospitalization regime (voluntary vs compulsory), brain imaging data, urine toxicological examination, treatment at the beginning and end of hospitalization, diagnosis. In line with the pandemic emergency hospital procedure, all patients were also tested for Severe Acute Respiratory Syndrome Corona Virus 2 (COVID-19) before being admitted to the ward and resulted negative.

During the pandemic and the ensuing lockdown, attempts were made to minimize the number of hospital admissions. For this purpose, tele-psychiatry was implemented in clinical practice. However, this was mostly effective in visiting patients with minor psychotic features for the first time (BPRS < 30) or following up patients already known to the psychiatric department. In the case of FEPs, the clinical picture were severe and did not allowed such management, as witnessed by the score of the BPRS (> than 30 for all the individuals); therefore, for this cluster of severely psychotic patients at their first contact with the mental health services, hospitalization was the only viable choice.

2.2. Clinical Assessment

In order to standardize evaluation criteria, we retrospectively retrieved all available clinical rating scales, and employed the following to assess the severity of illness: Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), Young Mania Rating Scale (YMRS) (Young et al., 1978), Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959), Global Assessment of Functioning (GAF) (Niv et al., 2007), and Clinical Global Impression (CGI) (Guy, 1976). Structured Clinical Interview for DSM-5 Personality Disorders (SCID-PD) (O'Donoghue et al., 2015) was only performed to patients who showed traits of personality disorders. Such psycometric tests are routinely performed in clinical practice for patients admitted into a psychiatric ward and therefore part of every patient's medical records.

2.3. Statistical analysis

Based on their ICD-10 diagnostic codes, patients were first grouped in substance-induced (F12.259, F14.259, F15.259), acute (F23, F31.2, F32.3) and chronic psychosis (F20.81, F22) and then re-grouped in substance-induced (F12.259, F14.259, F15.259), affective (F31.2, F32.3) vs non-affective psychosis (F23, F22, F20.81). The total score of each psychometric scale (HAM-A, HAM-D, YMRS, BPRS) was considered along with its absolute variation between admission and discharge.

The year of hospitalization was considered as the independent variable of interest for each statistical test conducted. A statistical significance threshold was set at $\alpha = 0.05$. For categorical variables χ^2 contingency table tests were conducted while for numerical ones Welch's t-tests for means comparisons were performed. Data cleaning and preprocessing was achieved using Julia 1.5.0 and statistical tests were carried out using R 4.0.2.

Non-parametric test (Mann-Whitney rank test) has also been performed to confirm the statistically significant difference in age and ΔHAM-A scores between the two samples, that are patients with FEP in 2019 and patients with FEP in 2020.

3. Results

Sociodemographic and clinical variables of the entire sample (N=62) and related subgroups are shown in Tables 1 and 2, respectively.

During the identified timeframe, 35 FEP patients were hospitalized in 2020 and 27 in 2019 (29,6% increase). Socio-demographic variables were found to largely overlap across the two samples, with no statistically significant difference observed for gender (p=0.224), education (p=0.946) and number of family members (p=0.292). In contrast, patients hospitalized for a FEP in 2020 were found to be significantly older (mean age: 43.5 ± 15.8 vs 34.0 ± 13.3, p=0.013; median age: 29.0 IQR 16.0 vs 45.0 IQR 26.5) (Figure 1), and to report significantly less substance abuse than those hospitalized the previous year (17.1% vs 59.3%, p=0.039) (Figure 2). Through non-parametric test, the statistically significant difference in age between the two samples was confirmed (p=0.006).

Table 1
Socio-demographic variables of the study sample according to the presence of FEP, stratified by year.

Variables	2019 FEP patients	2020 FEP patients
Number of patients	27	35
Age (years, mean ± SD, age range)	34.0 ± 13.3* (20-66)	43.5 ± 15.8*(18-73)
Gender (%)		
Male	55.5	40
Female	44.4	60
Education (years, mean ± SD)	13.6 ± 4.1	13.5 ±3.9
Number of family members (%)		
1 member	22.2	22.9
2 members	37.0	25.7
3-4 members	29.6	42.9
>5 members	11.1	8.6
Current substance abuse (%)		
Yes	59.3*	17.1*
None	40.7*	82.9*

Legend: Values for categorical and continuous variables are expressed in percentages and mean ± SD, respectively. FEP: first episode psychosis. Statistics: *p<.05

Table 2
Clinical variables of the study sample according to the presence of FEP, stratified by year.

	2019 FEP patients	2020 EFP patients
Psychosis subtype (%)		
Acute Psychosis	66.7	77.1
Chronic Psychosis	14.8	14.2
Substance-induced Psychosis	18.5	8.6
Psychosis subtype (%)		
Affective Psychosis	33.3	31.4
Induced Psychosis	18.5	8.6
Non-Affective Psychosis	48.1	60
Duration of Hospitalization (days, mean ± SD)	13.1 ± 6.9	12.3 ± 6.7
HAM-D (mean ± SD)		
Admission scores	17.4 ± 9.5 (n=19)	21.9 ± 12.4 (n=35)
Discharge scores	5.0 ± 2.5 (n=19)	4.6 ± 3.9 (n=35)
Admission-discharge variation	12.4 ± 7	17.3 ± 8.5
YMRS (mean ± SD)		
Admission scores	18.4 ± 11.4 (n=19)	15.3 ± 8.5 (n=35)
Discharge scores	4.7 ± 4.7 (n=19)	2.5 ± 2.5 (n=34)
Admission-discharge variation	13.7 ± 6.7	12.9 ±6
BPRS (mean ± SD)		
Admission scores	53.6 ± 13.6 (n=19)	60.5 ± 14.6 (n=35)
Discharge scores	24 ± 3.2 (n=19)	25.4 ± 4.5 (n=35)
Admission-discharge variation	29.6 ± 10.4	35.1 ± 10.1
HAM-A (mean ± SD)		
Admission scores	12.5 ± 9.8 (n=19)	18 ± 9.7 (n=35)
Discharge scores	4.4 ± 2.7 (n=19)	3.6 ± 2.4 (n=34)
Admission-discharge variation	8.1 ± 7.1*	14.6 ±7.3 *
CGI (mean ± SD)		
Gravity	4.4 ± 0.8 (n=19)	4.9 ± 0.9 (n=35)
Improvement	1.4 ± 0.6	1.5 ± 0.6

Legend: Values for categorical and continuous variables are expressed in percentages and mean ± SD, respectively. Boldface indicates parameters with significant differences between the two subgroups. FEP: First Episode Psychosis; HAM-D: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; BPRS: Brief Psychiatric Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; CGI: Clinical Global Impressions. Statistics: *p<.05.

The observed differences across subtypes of psychosis did not reach statistical significance (p=0.496): acute psychoses were 18 (66.7%) in 2019 versus 27 (77.1%) in 2020, chronic psychoses were 4 (14.8%) in 2019 versus 5 (14.2%) in 2020 and substance-induced psychoses 5 (18.5%) in 2019 versus 3 (8.6%) in 2020. Moreover, affective psychoses were 9 (33.3%) in 2019 versus 11 (31.4%) in 2020, substance-induced psychoses were 5 (18.5%) in 2019 versus 3 (8.6%) in 2020, and non-affective were 13 (48.1%) in 2019 versus 21 (60%) in 2020 (p=0.455). No difference was observed in the two samples in terms of duration of hospitalization (p=0.666) and psychometric assessment upon admission and discharge (HAM-D at admission: p=0.141; YMRS at admission: p=0.316; BPRS at admission: p=0.088; HAM-A at admission: p=0.054; HAM-D at discharge: p=0.672; YMRS at discharge: p=0.080; BPRS at discharge: p=0.204; HAM-A at discharge: p=0.297; ΔHAM-D: p=0.091; ΔYMRS: p=0.786; ΔBPRS: p=0.170), with the exception of HAM-A total score improvement (14.6 ±7.3 vs 8.1 ± 7.1, ΔHAM-A: p=0.025) (Figure 3). Through non-parametric test, the statistically significant difference in ΔHAM-A between the two samples was confirmed (p=0.007).

4. Discussion

Our study allowed to identify the characteristics of FEP cases that were hospitalized in the city of Milan during the COVID-19 pandemic and the consequent lockdown. In such an exceptional and stressful context, a 29,6% increase in psychiatric hospitalizations for incident psychosis cases was observed. Our preliminary data are in line with the available evidence, according to which distress related to the pandemic caused an increase in anxiety and depression (Salari et al., 2020), but also psychotic symptoms (Radua et al., 2018; Brown et al., 2020; D'Agostino et al., 2021).

Regarding the characteristics of psychotic episodes, the FEP cases admitted in 2020 did not show significant qualitative differences compared to those from the previous year, neither in terms of duration nor psychometric scores. However, some aspects of FEP patients admitted during the first wave of this pandemic, such as their relatively higher mean age (43.5 in 2020 vs 34.0 in 2019), appear noteworthy (Figure 1). This diametrically opposite trend to the pre-pandemic literature on FEP (Janssen et al., 2006) suggests a more stress-related pathogenesis in these individuals. This finding is in line with one previous case series of three female health care workers who experienced a FEP in their forties during the outbreak (Elliot, 2020).

Environmental risk factors are known to play a role in the development of psychosis. This occurs both for early environmental risk factors, which generally reduce the onset age of psychotic symptoms, but also for late environmental risk factors, to which the elderly are more vulnerable (Fusar-Poli et al., 2017). In terms of mental health, elder subjects are known to be more vulnerable to environmental stressors. Several explanatory hypotheses suggest co-occurring medical illness or less effective cognitive response strategies play a crucial role in such vulnerability (Janssen et al., 2006). Although the emergence of this frailty has typically been associated with anxiety and depression, cases of psychotic disorders have also been documented (Hashem et al., 2017; Van Assche et al., 2017). Late-onset psychosis represents heterogeneous clinical pictures, which are characterized by the late onset of schizophrenia-like symptoms (Suen et al., 2019). The impact that brain aging and cognitive dysfunctions have on these late psychotic onsets seems to correlate with pre-existing risk factors for developing psychosis (Van Assche et al., 2017). In particular, the onset of psychosis in elderly subjects is an entity that has been studied for its clinical overlap with cases of neurological relevance, such as prodromal symptoms of dementia (Fischer and Agüera-Ortiz, 2018). However, a recent review pointed out that only a small number of subjects with late-onset psychosis develop dementia in the ten years following the onset of psychiatric symptoms, perhaps suggesting a stress-related acceleration of brain aging might be implied rather than a neurodegenerative pathology (Van Assche et al., 2017).

The COVID-19 pandemic and the national lockdown was a relevant environmental stressor for a large portion of the Italian population. Social deafferentation and major lifestyle changes had an impact on
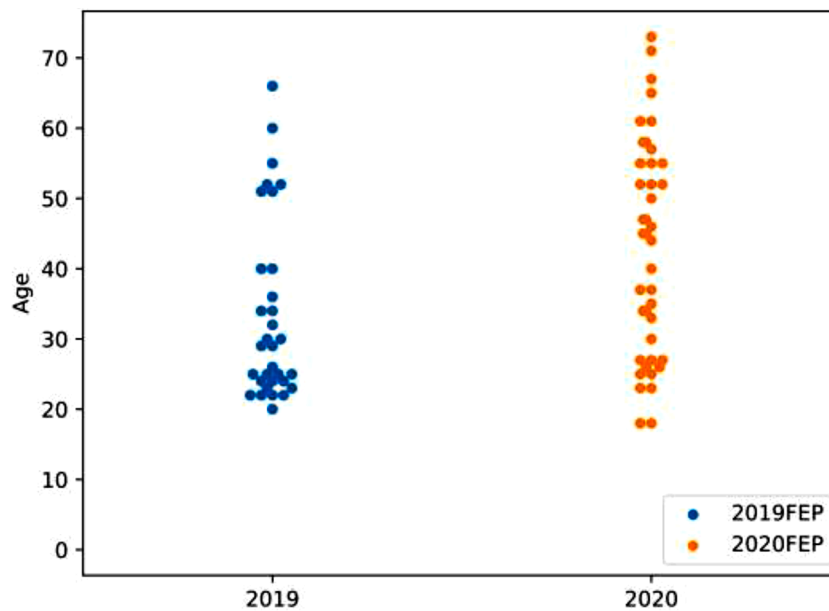
Figure 1. Age of patients hospitalized for FEPs in 2019 and in 2020
In Figure 1 it is possible to see the different age distribution of patients with FEP in 2019 and 2020. Patients with FEP in 2020 show a greater distribution of ages, which instead in patients with FEP in 2019 was mostly concentrated between 20 and 40 years.
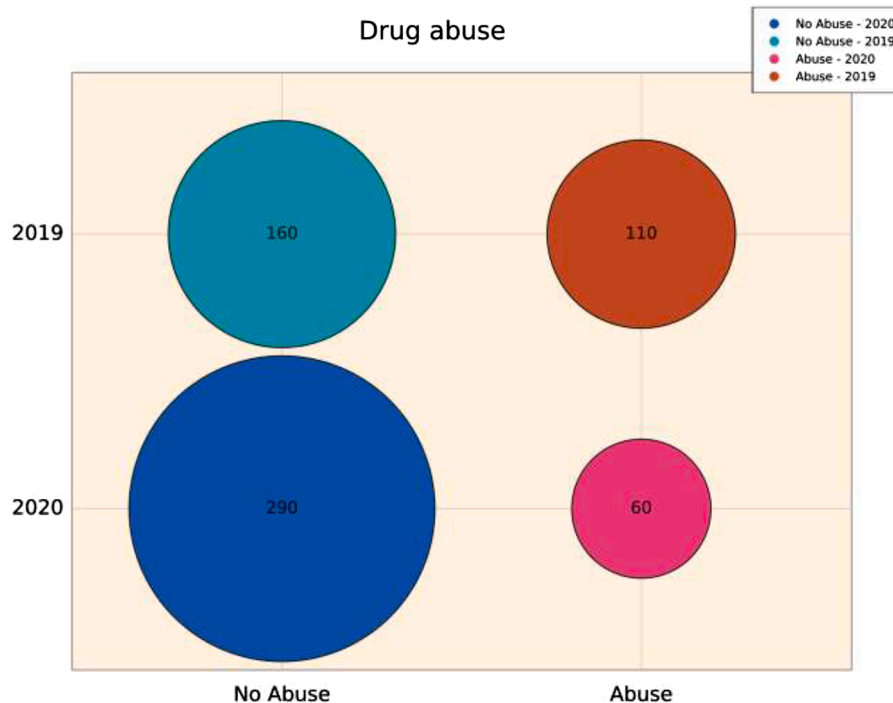

Figure 2. Substance abuse in patients hospitalized for FEPs in 2019 and in 2020
In Figure 2 it is possible to see the percentage of patients who, concomitantly with the development of FEP, abused substances. In 2020, among patients who developed FEP, there were fewer abusers than in 2019.

most individuals, who were unable to take advantage of their usual strategies for managing adversity (Torales et al., 2020). Although our findings cannot unequivocally explain the factors that sustained an increased vulnerability to psychosis in elder individuals, intense fear responses to the pandemic outbreak are likely to have played a role. On the one hand, elder individuals in the general population have physical pathologies that would have made the COVID-19 infection more serious (Perrotta et al., 2020). On the other, the elderly population was extensively described as more vulnerable to the development of serious

clinical pictures and death in media communication strategies (Perrotta et al., 2020). Undoubtedly, aging has been strongly associated with worse outcomes to COVID-19, with a significant increase in mortality for subjects over 65 years (Libertini et al., 2019).

Incident FEP cases observed during the pandemic presented relatively higher anxiety scores upon admission but, most significantly, increased anxiety-score responsivity to hospitalization. Whereas higher mean anxiety scores have previously been reported in elder samples of FEP patients (Wilson et al., 2020), we interpret the increased response to
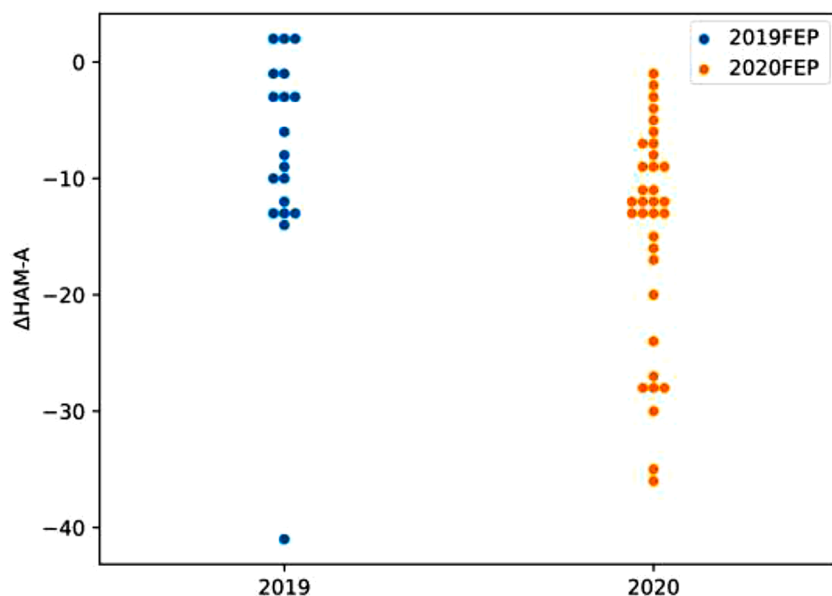
Figure 3. Differences in HAM-A score at admission and discharge in patients
hospitalized for FEPs in 2019 and in 2020
Patients underwent the HAM-A rating scale at admission and at discharge. The difference in the score obtained at discharge compared to admission (ΔHAM-A) determines the clinical improvement of the patient with regard to anxious symptoms. In Figure 3 it is possible to see the distribution of ΔHAM-A in patients with FEP hospitalized in 2019 and 2020. It is possible to graphically see how in 2020 the reduction in the HAM-A score was greater and more distribuited.

hospitalization as evidence of a stress-related pathogenesis in this population. The reduction of substance abuse in 2020 FEP patients is then a data of extreme interest (Figure 2). In the first place, it means that only a few of the cases observed were induced by substances and therefore most of them have only to be ascribed to the vulnerability-environment conjunction of the single individuals. The lower impact of substances in the onset of FEP may also have environmental reasons linked to the particular condition of the lockdown, such as the reduction of social gatherings and the difficulty in finding illicit psychoactive substances. Such evidence seems to place the FEPs arising in the period of COVID-19 pandemic as psychotic episodes with qualitative characteristics similar to the FEPs not resulting from periods of worldwide stress. The notable data seems to be that 2020 FEPs affect an older portion of the population with respect to the norm of FEPs (O'Donoghue et al., 2015).

The limitations of this study are related to the small sample size, the difficulty of establishing a clear etiological link between pandemic-related stress and the emerging psychosis, and the diagnostic variability of the psychotic episodes reported. The disparity of diagnoses is consistent with the difficulty in establishing the course of a potential disorder (Santesteban-Echarri et al., 2017) at the onset of a first psychotic episode (Nikolai and Weibell, 2019).

Although further studies are needed to confirm these preliminary data, our study suggests a moderate increase of psychotic episodes in the general population which might reflect the intense psychosocial stress of the ongoing pandemic. A detailed follow-up of the population over time is also necessary to confirm this hypothesis.

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CRediT authorship contribution statement

C.M. Esposito: Conceptualization, Data curation, Investigation, Writing - original draft. **A. D'Agostino:** Conceptualization, Investigation, Supervision, Writing - original draft. **B. Dell Osso:** Supervision. **A. Fiorentini:** Conceptualization, Supervision. **C. Prunas:** Conceptualization, Supervision. **A. Callari:** Conceptualization, Supervision. **L. Oldani:** Writing - review & editing. **E. Fontana:** Conceptualization, Data curation, Investigation. **G. Gargano:** Conceptualization, Data curation, Investigation. **B. Viscardi:** Conceptualization, Data curation, Investigation. **B. Giordano:** Conceptualization, Data curation, Investigation. **S D'Angelo:** Conceptualization, Data curation, Investigation. **F. Wiedenmann:** Data curation, Investigation. **M. Macellaro:** Data curation, Investigation, Writing - original draft. **F. Giorgetti:** Data curation, Investigation. **Ne Turtulici:** Formal analysis. **O. Gambini:** Supervision. **P. Brambilla:** Conceptualization, Supervision, Writing - review & editing.

Declaration-of-Competing-Interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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References

Barbisch, D., Koenig, K.L., Shih, F.-Y., 2015. Is There a Case for Quarantine? Perspectives from SARS to Ebola. Disaster Med Public Health Prep 9 (5), 547–553. https://doi.org/10.1017/dmp.2015.38.

Brooks, S.K., Webster, R.K., Smith, L.E., Woodland, L., Wessely, S., Greenberg, N., Rubin, G.J., 2020. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 395 (10227), 912–920. https://doi.org/10.1016/S0140-6736(20)30460-8.

Brown, E., Gay, R., Lo Monaco, S., O'Donoghue, B., Nelson, B., Thompson, A., Francey, S., McGorry, P., 2020. The potential impact of COVID-19 on psychosis: A rapid review of contemporary epidemic and pandemic research. Schizophr Res 6. https://doi.org/10.1016/j.schres.2020.05.005.

Chan, S.M.S., Chiu, F.K.H., Lam, C.W.L., Leung, P.Y.V., Conwell, Y., 2006. Elderly suicide and the 2003 SARS epidemic in Hong Kong. Int J Geriatr Psychiatry 21 (2), 113–118. https://doi.org/10.1002/gps.1432.

D'Agostino, A., Demartini, B., Cavallotti, S., Gambini, O., 2021. Mental health services in Italy during the COVID-19 outbreak. Lancet Psychiat 7 (5), 385–387. https://doi.org/10.1016/S2215-0366(20)30133-4.

D'Agostino, A., D'Angelo, S., Giordano, B., Cigognini, A.C., Chirico, M.L., Redaelli, C., Gambini, O., 2020. Brief Psychotic Disorder during the national lockdown in Italy: an emerging clinical phenomenon of the coronavirus. Schizophr Bull 6, sbaa112. https://doi.org/10.1093/schbul/sbaa112.

DeLisi, L.E., 2021. A commentary revisiting the viral hypothesis of schizophrenia: Onset of a schizophreniform disorder subsequent to SARS CoV-2 infection. Psychiatry Res 295, 113573. https://doi.org/10.1016/j.psychres.2020.113573.

Druss, B.G., 2020. Addressing the COVID-19 Pandemic in Populations With Serious Mental Illness. JAMA Psychiatry 1 (9), 891–892, 770.1001/jamapsychiatry.2020.0894.

Elliot Jr, B.M., 2020. Brief Psychotic Disorder Triggered by Fear of Coronavirus? Psychiatr Times 37 (5). https://doi.org/10.1016/j.psym.2020.05.012.

Finatti, F., Pigato, G., Pavan, C., Toffanin, T., Favaro, A., 2020. Psychosis in Patients in COVID-19-Related Quarantine: A Case Series. Prim Care Companion CNS Disord 14 (3), 20l02640. https://doi.org/10.4088/PCC.20l02640, 22.

Fiorillo, A, Gorwood, P, 2020. The consequences of the COVID-19 pandemic on mental health and implications for clinical practice. Eur Psychiat 63(1), e32.

Fischer, C.E., Agüera-Ortiz, L., 2018. Psychosis and dementia: risk factor, prodrome, or cause? Int Psychogeriatr 30 (2), 209–219. https://doi.org/10.1017/S1041610217000874.

Fusar-Poli, P., Tantardini, M., De Simone, S., Ramella-Cravaro, V., Oliver, D., Kingdon, J., Kotlicka-Antczak, M., Valmaggia, L., Lee, J., Millan, M.J., Galderisi, S., Balottin, U., Ricca, V., McGuire, P., 2017. Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. Eur Psychiatry 40, 65–75. https://doi.org/10.1016/j.eurpsy.2016.09.003.

Fusar-Poli, P., Brambilla, P., Solmi, M., 2020. Learning from COVID-19 pandemic in northen italy: Impact on mental health and clinical care. J Affect Disord 275, 78–79. https://doi.org/10.1016/j.jad.2020.06.028, 2020 Jul 2.

Galea, Merchant, Lurie, 2020. The Mental Health Consequences of COVID–19 and Physical Distancing: The Need for Prevention and Early Intervention. JAMA Intern Med 180(6), 817–818.

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. US Department of Heath, Education, and Welfare Public Health Service Alcohol. Drug Abuse, and Mental Health Administration, Rockville.

Hamilton, M., 1959. The assessment of anxiety states by rating. Br J Med Psychol 32, 50–55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x.

Hamilton, M., 1960. A rating scale for depression. Journal of Neurology. Neurosurgery and Psychiatry 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Hashem, A.H., Nasreldin, M., Gomaa, M.A., Khalaf, O.O., 2017. Late versus Early Onset Depression in Elderly Patients: Vascular Risk and Cognitive Impairment. Curr Aging Sci 10 (3), 211–216. https://doi.org/10.2174/1874609810666170404105634.

Heinz, A., Murray, G.K., Schlagenhauf, F., Sterzer, P., Grace, A.A., Waltz, J.A., 2019. Towards a Unifying Cognitive, Neurophysiological, and Computational Neuroscience Account of Schizophrenia. Schizophr Bull 11 (5), 1092–1100. https://doi.org/10.1093/schbul/sby154, 45.

Kawhola, W., Nordta, C., 2020. COVID-19, unemployment, and suicide. Lancet Psychiatry 7 (5), 389–390. https://doi.org/10.1016/S2215-0366(20)30141-3.

Janssen, J., Beekman, A.T., Comijs, H.C., Deeg, D.J., Heeren, T.J., 2006. Late-life depression: the differences between early- and late-onset illness in a community-based sample. Int J Geriatr Psychiatry 21 (1), 86–93. https://doi.org/10.1002/gps.1428.

Libertini, G., Corbi, G., Cellurale, M., Ferrara, N., 2019. Age-related dysfunctions: evidence and relationship with some risk factors and protective drugs. Biochemistry (Mosc) 84, 1442–1450. https://doi.org/10.1134/S0006297919120034.

Mizrahi, R., 2016. Social Stress and Psychosis Risk: Common Neurochemical Substrates? Neuropsychopharmacology 41 (3), 666–674. https://doi.org/10.1038/npp.2015.274.

Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. Br J Psychiatry 134, 382–389. https://doi.org/10.1192/bjp.134.4.382.

Nikolai, A., Weibell, M.A., 2019. The outcome of early intervention in first episode psychosis. Int Rev Psychiatry 31 (5-6), 413–424. https://doi.org/10.1080/09540261.2019.1643703.

Niv, N., Cohen, A.N., Sullivan, G., Young, A.S., 2007. The MIRECC version of the Global Assessment of Functioning scale: Reliability and validity. Psychiatric Services 58, 529–535. https://doi.org/10.1176/ps.2007.58.4.529.

O'Donoghue, B., Lyne, J., Madigan, K., Lane, A, Turner, N., O'Callaghan, E., Clarke, M., 2015. Environmental factors and the age at onset in first episode psychosis. Schizophr Res 168 (1-2), 106–112. https://doi.org/10.1016/j.schres.2015.07.004.

Overall, J.E., Gorham, D.R., 1962. The Brief Psychiatric Rating Scale. Psycol Rep. https://doi.org/10.2466/pr0.1962.10.3.799, 10:799.

Qiu, J., Shen, B., Zhao, M., Zhen, W., Xie, B., Xu, Y., 2020. A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. Gen Psychiatr 33, e100213. https://doi.org/10.1136/gpsych-2020-100213.

Perrotta, F., Corbi, G., Mazzeo, G., Boccia, M., Aronne, L., D'Agnano, V., Komici, K., Mazzarella, G., Parrella, R., Bianco, A., 2020. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging Clin Exp Res 32 (8), 1599–1608. https://doi.org/10.1007/s40520-020-01631-y.

Radua, J., Ramella-Cravaro, V., Ioannidis, J.P.A., Reichenberg, A., Phiphopthatsanee, N., Amir, T., Yenn Thoo, H., Oliver, D., Davies, C., Morgan, C., McGuire, P., Murray, R. M., Fusar-Poli, P., 2018. What Causes Psychosis? An Umbrella Review of Risk and Protective Factors. World Psychiatry. 17 (1), 49–66. https://doi.org/10.1002/wps.20490.

Rogers, J.P., Chesney, E., Oliver, D., Pollak, T.A., McGuire, P., Fusar-Poli, P., Zandi, M.S., Lewis, G., David, A.S., 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiat 7 (7), 611–627. https://doi.org/10.1016/S2215-0366(20)30203-0.

Salari, N., Hosseinian-Far, A., Jalali, R., Vaisi-Raygani, A., Rasoulpoor, S., Mohammadi, M., Rasoulpoor, S., Khaledi-Paveh, B., 2020. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Global Health 16, 57. https://doi.org/10.1186/s12992-020-00589-w.

Santesteban-Echarri, O., Paino, M., Rice, S., González-Blanch, C., McGorry, P., Gleeson, J., Alvarez-Jimenez, M., 2017. Predictors of functional recovery in first-episode psychosis: A systematic review and meta-analysis of longitudinal studies. Clin Psychol Rev 58, 59–75. https://doi.org/10.1016/j.cpr.2017.09.007.

Shanbour, A., Khalid, Z., Fana, M., 2020. Psychosis and Infodemic Isolation Resulting in First Inpatient Hospitalization During the COVID-19 Pandemic A Case Series. Prim Care Companion CNS Disord 4 (3), 20l02649. https://doi.org/10.4088/PCC.20l02649, 22.

Sher, L., 2020. COVID-19, anxiety, sleep disturbances and suicide. Sleep Med 70, 124. https://doi.org/10.1016/j.sleep.2020.04.019.

Sher L., 2020. The impact of the COVID-19 pandemic on suicide rates. QJM. 15;hcaa202. doi:10.1093/qjmed/hcaa202.

Suen, YN, Wong, SMY, Hui, CLM, Chan, SKW, Lee, EHM, Chang, WC, Chen, EYH, 2019 Aug-Sep. Late-onset psychosis and very-late-onset-schizophrenia-like-psychosis: an updated systematic review. Int Rev Psychiatry 31 (5-6), 523–542 doi: 10.1080/09540261.2019.1670624.

Torales, J., O Higgins, M., Castaldelli-Maia, J.M., Ventriglio, A., 2020. The outbreak of COVID-19 coronavirus and its impact on global mental health. Int J Soc Psychiatry 66 (4), 317–320. https://doi.org/10.1177/0020764020915212.

Van Assche, L., Morrens, M., Luyten, P., Van de Ven, L., Vandenbulcke, M., 2017. The neuropsychology and neurobiology of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: A critical review. Neurosci Biobehav Rev 83, 604–621. https://doi.org/10.1016/j.neubiorev.2017.08.024.

Vindegaard, N., Eriksen Benros, M., 2020. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. Brain Behav Immun 30 (20), 30954–30955. https://doi.org/10.1016/j.bbi.2020.05.048. S0889-1591.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133, 429–435. https://doi.org/10.1192/bjp.133.5.429.

Wilson, R.S., Yung, A.R., Morrison, A.P., 2020. Comorbidity rates of depression and anxiety in first episode psychosis: A systematic review and meta-analysis. Schizophrenia Research 216, 322–329. https://doi.org/10.1016/j.schres.2019.11.035.

Zulkifli, N.A., Sivapatham, S., Guan, N.C., 2020. Brief Psychotic Disorder in Relation to Coronavirus, COVID-19 Outbreaks: A Case Report. Malaysian Journal of Psychiatry 29, 1. https://doi.org/10.1016/j.schres.2020.05.005.