LIFETIME PSYCHIATRIC COMORBIDITY AND DIAGNOSTIC TRAJECTORIES IN AN ITALIAN PSYCHIATRIC SAMPLE

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Abstract

Objective: Comorbidity in psychiatric patients has been widely examined in the literature, enucleating the role in misinterpretation of symptom's root in a multi-disease background, as well as the impact on the quality of life, outcome, and healthcare effects. This research aimed to examine, in an Italian population of psychiatric patients, the diagnostic continuum in the context of lifetime psychiatric comorbidity, assessing possible differences related to the onset disorder.

Method: A retrospective analysis of medical records of 458 subjects, in which various psychiatric diagnoses were represented and categorized in 16 nosographic classes, was conducted.

Results: Results showed that "Bipolar disorder" (22.06%) was the most frequent diagnosis, "Eating disorder" had the earliest age onset (Mean age years = 16 ± 1.41), and "Schizophrenia" showed the longest disease duration (Mean years = 24.20±12.76). Moreover, 54,4% of the final sample presented at least one psychiatric comorbidity in disease history, while "Other personality disorders" was the most comorbidity-associated diagnosis, representing 29% of all the cases with more than 3 past diagnoses. Heterotypic transition was observed in fairly all considered onset diagnoses, exception made for "Schizophrenia" with 75% of the subjects showing homotypic progression.

Conclusions: Our results suggest a tendency to make multiple diagnoses over psychiatric patients' lifetime in the majority of cases, often escaping from the original onset nosographic domain. More generally, our findings agree with a broad consensus that describes psychiatric symptomatic dimensions rather overlapped and correlated with each other, leading to a more transdiagnostic clinical approach.

Key words: comorbidity, diagnostic trajectories, heterotypic pattern, homotypic pattern

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A large amount of literature found out that from one quarter to one-third of the population suffered from psychiatric disorders in the past year and comorbidity has been evaluated to be present roughly up to 45% of them, i.e. it is a wide-spread occurrence (Bijl, Ravelli, & van Zessen, 1998; Andrews, Slade, & Issakidis, 2002; Jacobi, Wittchen, Hölting, Höfler, Pfister & Lieb, 2004; Kessler, Avenevoli, & McLaughlin, 2012; Plana-Ripoll, Pedersen, Holtz, Benros, Dalsgaard, De Jonge & Gunn, 2019). The term "comorbidity" means the coexistence of different diseases in an individual (Klerman, 1990; Strakowski, Keck, McElroy, Lonczak, & West, 1995; Andrews, 1996; Kraemer, Shrout, & Rubio-Stipec, 2007). Some evidence over the last three decades has established that comorbidity is the rule rather than the exception among patients (Goldberg & Fagin-Jones, 2004). This condition led to a debate about the interpretation of its high rates, as it has been proposed as a way to cluster diseases, based on the assumption that two disorders occur more frequently together since they have a common root-cause (Andrews, Goldberg, Krueger, Carpenter, Hyman, Sachdev & Pine, 2009). Comorbidity is often investigated by studying composite measures defined on two sets of items (i.e. correlation between total scores on checklists) or two diagnoses. This kind of methodology assumes that symptoms are viewed as merely passive indicators of latent conditions rather than properties with their casual relevance. Therefore, when a symptom arises, it can cause other symptoms on their own. According to this approach, symptoms are not viewed as indicators of latent conditions, but as components in a network; comorbidity is hypothesized to result from direct association among symptoms of multiple disorders. Thus, direct relations among symptoms could exist, and, as a result of this, we could find differences in how comorbidity occurs

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and then develops in each patient. (Borsboom, Cramer, Schmittmann, Epskamp, & Waldorp, 2011). Since the rate of comorbidity has been studied, it appears to be useful in the clinical practice as it counts as a criterion to analyze the risks and clinical factors among different diseases (Andrews et al., 2009). Nevertheless, comorbidity raised a problem since it indicates the tough task to diagnose associated disorders, in other words the difference between a symptom of a disorder and another distinct disease can be misunderstood because in this field boundaries among disorders are often shaded (Kendell & Jablensky, 2003). The critical question is whether psychiatric syndromes are separated from one another, and from normality, by "zones of rarity" or whether they are simply not connected to each other in a multidimensional area where variation in symptoms and etiology is not continuous (Kendell & Jablensky, 2003). Also, comorbidity has been investigated for the impact on the quality of life, outcome, and health-care effects: some evidence proved that it is associated with a negative outcome and functional disabilities (Schoevers, Deeg, van Tilburg, & Beekman, 2005). For instance, the presence of comorbid diseases is linked with longer hospitalization, higher costs because of the amount of care needed. Spoorthy et al. (2019) pointed out that comorbidity led patients to severe illness and worse acute episodes; furthermore, it is associated with longer episodes and poorer remission and recovery, with nuanced symptoms. Most of all it causes a poorer quality of life and poorer treatment response, delayed diagnosis, severe medication side-effect and nonadherence with treatment (Spoorthy, Chakrabarti, & Grover, 2019).

Based on this background, this research aimed to examine, in an Italian population of psychiatric patients, the diagnostic continuum in the context of lifetime psychiatric comorbidity, assessing possible differences related to the onset disorder.

Materials and methods

A retrospective analysis of the medical records of the Psychiatric Unit of the University Hospital of Messina - Italy, of the period January 2014 - December 2018 was conducted. Psychiatric disorders have been categorized in 16 nosographic diagnosis: 1) Schizophrenia; 2) Other psychosis; 3) Bipolar Disorder; 4) Major Depressive Disorder; 5) Panic Disorder; 6) Obsessive-compulsive Disorder; 7) Other Anxiety Disorders; 8) Borderline Personality Disorder; 9) Other Personality Disorders; 10) Eating Disorders; 11) Drug Addiction; 12) Impulse Control Disorder; 13) Neurocognitive Disorder; 14) Sleep Disorders; 15) Dissociative Disorder; 16) Pathological Gambling Disorder.

Descriptive analyses were used to illustrate the characteristics of the sample. The discrete and nominal variables were described through frequencies and percentages and the quantitative variables were expressed in terms of mean and standard deviation (S.D.). A regression model of Cox proportional Hazard Ratio was used to determine the risk that patients with an onset diagnosis could develop other disorders on the lifetime since onset disorder. The risk was reported as hazard ratios (HRs) with 95% confidence intervals (95% CI) and the onset diagnosis was chosen as independent variable and the current diagnosis as dependent variable (Presence/Absence). Cox regression analysis was carried out on the whole sample, stratifying by gender. All the data were recorded electronically, and statistical analyses were carried out using the Stata Statistical Software: Release 15 (Stata Corp LP, College Station, TX, USA).

Results

Sample features

The final sample includes 485 subjects, 259 females (53.4%) and 226 males (46.6%), aged between 18 and 82 years old (Mean age ± S.D. = 47.1 ± 14.9 years), with a mean disease duration of 17.1 ± 13.5 years.

Table 1 shows the distribution of actual diagnoses, age of onset, and disease duration of the whole sample. Data analysis highlighted Bipolar Disorder as the most common disease (22.06%), followed by Other

Table 1. *Frequency of current diagnosis, age of onset, and disease duration in 485 patients*

	Frequency		Age of onset (Years)		Disease duration (Years)	
Current diagnosis	N	%	Mean	SD	Mean	SD
Schizophrenia	35	7.22	22.34	7.50	24.20	12.76
Other Psychoses	103	21.24	27.09	15.14	13.47	11.61
Bipolar disorder	107	22.06	30.90	14.15	21.38	14.30
Depression	82	16.91	37.80	16.56	17.27	13.83
Obsessive-compulsive Disorder	3	0.62	33.00	14.18	15.33	19.73
Other anxiety disorders	1	0.21	44.00	0.00	1	-
Borderline Personality Disorder	35	7.22	19.44	9.49	17.24	10.93
Other personality disorder	105	21.65	29.93	13.90	15.59	12.76
Eating disorders	2	0.41	16.00	1.41	12.00	12.73
Substance abuse	1	0.21	50.00	0.00	1	-
Impulse control disorder	3	0.62	44.00	12.77	17.67	28.87
Neurocognitive disorder	5	1.03	44.80	25.30	14.20	18.93
Dissociative disorder	3	0.62	35.00	7.00	1	-
Total	Total 485	100.00	29.89	15.06	17.29	13.51

Personality Disorders (21.65%) and Other psychosis (21.24%); Sleep Disorders, Pathological Gambling Disorder and Panic Disorders were not present.

Regarding the age of onset, we have found the earliest onset in Eating Disorders (Mean age = 16 ± 1.41), followed by Borderline Personality Disorder (Mean age = 19.44 ± 9.49) and Schizophrenia (Mean age = 22.34 ± 7.50). Concerning disease duration, Schizophrenia was the longest-lasting (Mean years = 24.20 ± 12.76), followed by Bipolar Disorder (Mean years = 21.38 ± 14.30).

Comorbidity

Table 2 reports the psychiatric comorbidity related to the current diagnosis.

Data analysis showed that 54.4% (n = 264) of the sample presented at least one psychiatric comorbidity in his disease history, while the remaining 45.6% (n = 221) received a unique diagnosis. Regarding current diagnosis, "Other Personality Disorders" was the most comorbidity-associated diagnosis, representing 29% of all the cases with more than 3 past diagnoses, followed by "Borderline Personality Disorder" (22.58%), "Bipolar Disorder" (16.13%) and "Major Depressive Disorder" (16.13%).

Diagnosis progression

Table 3 reports the frequency of current diagnosis according to onset disorder.

Data analysis showed heterotypic transition diagnostic patterns for all the onset diagnoses considered, suggesting a tendency to make multiple diagnoses over psychiatric patients' lifetime. A diagnostic trend exception (homotypic pattern) emerged for "Schizophrenia" patients, with 75% of the subjects continued to receive a diagnosis in the psychotic disorder's spectrum (Schizophrenia/Other psychotic disorders) life-time.

In order to determine the patient's risk to develop other disorders on the lifetime since onset disorder, a Cox proportional hazards regression models was performed (**table 4**). In lifetime psychiatric comorbidities, the risk of developing Schizophrenia in patients who had Other psychotic disorders as onset diagnosis was significantly higher (HR 6.96, 95% CI 1.10 to 44.22, p=0.040). The results showed a lower risk of developing Other psychotic disorders in those who had Other psychotic disorders also as onset diagnosis: HR 0.10, 95% CI 0.01 to 0.89, p=0.039. Women with onset diagnosis of Bipolar Disorders had a high risk to develop Borderline Personality Disorder (HR 29.82, 95% CI 1.07 to 828.29, p=0.045). Onset diagnosis of depression was significantly associated with a lower risk both of developing Other psychotic disorders and of continuing to be depressed (HR 0.39, 95% CI 0.17 to 0.91, p=0.029; HR 0.34, 95% CI 0.14 to 0.85, p=0.021, respectively). These results were confirmed also after stratification by sex. In patients who had been diagnosed with Other Personality Disorders, the risk of

Table 2. *Sample stratified by presence and number of previous diagnoses*

	Previous Diagnoses			Number of previous diagnoses			
Current diagnosis, n (%)	Total N=485	Absent n=221	Present n=264	1 previos diagnoses n=120	2 previous diagnoses n=74	3 previous diagnoses n=39	More than 3 previous diagnoses n=31
Schizophrenia	35 (7.22)	9 (4.07)	26 (9.85)	10 (8.33)	9 (12.16)	6 (15.38)	1 (3.23)
Other Psychoses	103 (21.24)	64 (28.96)	39 (14.77)	26 (21.67)	9 (12.16)	2 (5.13)	2 (6.45)
Bipolar disorder	107 (22.06)	42 (19.00)	65 (24.62)	22 (18.33)	24 (32.43)	14 (35.90)	5 (16.13)
Depression	82 (16.91)	44 (19.91)	38 (14.39)	19 (15.83)	8 (10.81)	6 (15.38)	5 (16.13)
Obsessive-compulsive Disorder	3 (0.62)	1 (0.45)	2 (0.76)	0 (0.00)	0 (0.00)	1 (2.56)	1 (3.23)
Other anxiety disorders	1 (0.21)	1 (0.45)	0 (0.00)	-	-	-	-
Borderline Personality Disorder	35 (7.22)	10 (4.52)	25 (9.47)	9 (7.50)	5 (6.76)	4 (10.26)	7 (22.58)
Other personality disorder	105 (21.65)	39 (17.65)	66 (25.00)	32 (26.67)	19 (25.68)	6 (15.38)	9 (29.03)
Eating disorders	2 (0.41)	1 (0.45)	1 (0.38)	1 (0.83)	0 (0.00)	0 (0.00)	0 (0.00)
Substance abuse	1 (0.21)	1 (0.45)	0 (0.00)	-	-	-	-
Impulse control disorder	3 (0.62)	2 (0.90)	1 (0.38)	1 (0.83)	0 (0.00)	0 (0.00)	0 (0.00)
Neurocognitive disorder	5 (1.03)	4 (1.81)	1 (0.38)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.23)
Dissociative disorder	3 (0.62)	3 (1.36)	0 (0.00)	-	-	-	-

Table 3. *Frequency distribution of current diagnoses by the onset diagnosis*

Onset diagnosis	TOTAL N=264	Current diagnoses	n (%)
Schizophrenia	8 (3.03)	Schizophrenia	1 (12.50)
		Other Psychoses	5 (62.50)
		Bipolar disorder	1 (12.50)
		Other personality disorder	1 (12.50)
Other Psychoses	25 (9.47)	Schizophrenia	9 (36.00)
		Other Psychoses	2 (8.00)
		Bipolar disorder	3 (12.00)
		Depression	3 (12.00)
		Borderline Personality Disorder	1 (4.00)
		Other personality disorder	6 (24.00)
		Impulse control disorder	1 (4.00)
Bipolar disorder	22 (8.33)	Other Psychoses	4 (18.18)
		Bipolar disorder	5 (22.73)
		Depression	3 (13.64)
		Borderline Personality Disorder	5 (22.73)
		Other personality disorder	5 (22.73)
Depression	102 (38.64)	Schizophrenia	8 (7.84)
		Other Psychoses	12 (11.76)
		Bipolar disorder	31 (30.39)
		Depression	10 (9.80)
		Obsessiveness disorder	1 (0.98)
		Borderline Personality Disorder	8 (7.84)
		Other personality disorder	32 (31.37)
Panic disorder	9 (3.41)	Schizophrenia	1 (11.11)
		Bipolar disorder	2 (22.22)
		Depression	1 (11.11)
		Borderline Personality Disorder	1 (11.11)
		Other personality disorder	4 (44.44)
Obsessive-compulsive Disorder	19 (7.20)	Schizophrenia	1 (5.26)
		Other Psychoses	5 (26.32)
		Bipolar disorder	3 (15.79)
		Depression	4 (21.05)
		Other personality disorder	4 (21.05)
		Eating disorders	1 (5.26)
		Neurocognitive disorder	1 (5.26)
Other anxiety disorders	19 (7.20)	Schizophrenia	2 (10.53)
		Bipolar disorder	5 (26.32)
		Depression	4 (21.05)
		Obsessiveness disorder	1 (5.26)
		Borderline Personality Disorder	2 (10.53)
		Other personality disorder	5 (26.32)
Borderline Personality Disorder	6 (2.27)	Other Psychoses	3 (50.00)
		Bipolar disorder	2 (33.33)
		Depression	1 (16.67)
Other personality disorder	19 (7.20)	Schizophrenia	1 (5.26)
		Other Psychoses	3 (15.79)
		Bipolar disorder	3 (15.79)
		Depression	10 (52.63)
		Borderline Personality Disorder	2 (10.53)
Eating disorders	8 (3.03)	Schizophrenia	1 (12.50)
		Other Psychoses	1 (12.50)
		Bipolar disorder	3 (37.50)
		Borderline Personality Disorder	3 (37.50)
Substance abuse	8 (3.03)	Bipolar disorder	2 (25.00)
		Borderline Personality Disorder	2 (25.00)
		Other personality disorder	4 (50.00)
Impulse control disorder	6 (2.27)	Other Psychoses	1 (16.67)
		Borderline Personality Disorder	1 (16.67)
		Other personality disorder	4 (66.67)
Neurocognitive disorder	7 (2.65)	Schizophrenia	2 (28.57)
		Other Psychoses	3 (42.86)
		Bipolar disorder	1 (14.29)
		Other personality disorder	1 (14.29)
Sleep disorder	5 (1.89)	Bipolar disorder	3 (60.00)
		Depression	2 (40.00)
Pathological gambling disorder	1 (0.38)	Bipolar disorder	1 (100.00)

Table 4. *Estimate of hazard ratio by Cox proportional hazards regression models, risk of patients with onset diagnosis could develop other disorders*

		All patients			Males			Females		
Onset diagnosis	**Current diagnoses**	**HR°**	**95% CI**	**p-value**	**HR***	**95% CI**	**p-value**	**HR***	**95% CI**	**p-value**
Schizophrenia	Other Psychoses	0.55	0.13 to 2.39	0.426	0.57	0.13 to 2.51	0.456	-	-	-
Other Psychoses	Schizophrenia	**6.96**	1.10 to 44.22	**0.040**	4.63	0.35 to 60.90	0.244	8.26	0.57 to 119.35	0.121
	Other Psychoses	**0.10**	0.01 to 0.89	**0.039**	-	-	-	0.24	0.02 to 2.46	0.231
	Bipolar disorder	0.42	0.09 to 1.95	0.267	0.53	0.53 to 5.50	0.601	0.38	0.05 to 3.08	0.364
	Depression	0.35	0.07 to 1.80	0.210	-	-	-	0.54	0.09 to 3.13	0.494
	Other personality disorder	2.21	0.53 to 9.22	0.277	2.35	0.25 to 22.32	0.456	1.69	0.25 to 11.34	0.589
Bipolar disorder	Other Psychoses	0.52	0.14 to 1.94	0.328	0.79	0.11 to 5.61	0.815	0.42	0.07 to 2.61	0.353
	Bipolar disorder	0.40	0.10 to 1.57	0.189	0.92	0.05 to 15.90	0.953	0.30	0.06 to 1.54	0.151
	Depression	0.42	0.11 to 1.55	0.190	0.56	0.05 to 5.78	0.625	0.37	0.07 to 1.81	0.217
	Borderline Personality Disorder	5.37	0.66 to 43.88	0.117	-	-	-	**29.82**	1.07 to 828.29	**0.045**
	Other personality disorder	2.52	0.37 to 16.99	0.342	-	-	-	1.58	0.20 to 12.65	0.666
Depression	Schizophrenia	0.58	0.11 to 3.06	0.517	1.42	0.04 to 56.77	0.853	0.77	0.10 to 5.84	0.799
	Other Psychoses	**0.39**	0.17 to 0.91	**0.029**	0.51	0.15 to 1.70	0.271	**0.29**	0.09 to 0.94	**0.039**
	Bipolar disorder	0.79	0.39 to 1.60	0.515	1.01	0.28 to 3.59	0.998	0.69	0.29 to 1.63	0.393
	Depression	**0.34**	0.14 to 0.85	**0.021**	0.38	0.04 to 4.14	0.429	**0.30**	0.11 to 0.87	**0.026**
	Borderline Personality Disorder	2.33	0.50 to 10.83	0.279	-	-	-	7.83	0.75 to 81.41	0.085
	Other personality disorder	1.25	0.58 to 2.70	0.576	3.16	0.77 to 12.93	0.110	0.91	0.35 to 2.37	0.850
Panic disorder	Schizophrenia	1.22	0.08 to 18.67	0.887	-	-	-	4.54	0.13 to 163.33	0.408
	Depression	0.61	0.05 to 7.05	0.693	-	-	-	-	-	-
	Borderline Personality Disorder	1.03	0.05 to 19.60	0.938	-	-	-	7.97	0.28 to 228.08	0.225
	Other personality disorder	0.96	0.22 to 4.21	0.959	2.98	0.29 to 31.22	0.361	0.46	0.05 to 4.20	0.494
Obsessive-compulsive Disorder	Other Psychoses	0.43	0.09 to 2.09	0.294	0.50	0.10 to 2.55	0.404	-	-	-
	Bipolar disorder	0.60	0.16 to 2.28	0.450	0.37	0.04 to 3.47	0.382	0.92	0.17 to 4.96	0.925
	Depression	1.59	0.40 to 6.33	0.513	8.28	0.60 to 114.81	0.115	0.38	0.03 to 4.70	0.448
	Other personality disorder	1.40	0.24 to 8.31	0.709	0.88	0.08 to 10.26	0.918	2.60	0.22 to 31.38	0.452
Other anxiety disorders	Schizophrenia	0.81	0.07 to 9.71	0.869	-	-	-	1.37	0.07 to 26.55	0.834
	Bipolar disorder	0.45	0.12 to 1.74	0.246	0.40	0.06 to 2.50	0.328	0.57	0.06 to 5.24	0.620
	Depression	2.08	0.40 to 10.69	0.381	2.53	0.14 to 45.22	0.528	3.32	0.30 to 36.23	0.326
	Borderline Personality Disorder	1.10	0.06 to 19.84	0.948	-	-	-	-	-	-
	Other personality disorder	0.80	0.22 to 2.88	0.733	0.62	0.06 to 6.54	0.690	0.98	0.21 to 4.58	0.977
Borderline Personality Disorder	Depression	1.10	0.10 to 12.56	0.941	-	-	-	1.11	0.10 to 12.96	0.932
Other personality disorder	Schizophrenia	0.38	0.03 to 5.07	0.465	2.56	0.06 to 118.40	0.631	-	-	-
	Other Psychoses	0.36	0.04 to 2.99	0.344	0.53	0.06 to 4.73	0.572	-	-	-
	Bipolar disorder	0.69	0.16 to 3.00	0.621	0.37	0.03 to 4.81	0.450	0.96	0.16 to 5.83	0.965
	Depression	**4.07**	1.18 to 14.00	**0.026**	7.38	0.98 to 55.81	0.053	3.68	0.60 to 22.60	0.160

Table 4. *Continue*

	Borderline Personality Disorder	3.46	0.33 to 36.58	0.302	-	-	-	2.72	0.09 to 78.64	0.561
Eating disorders	Bipolar disorder	1.34	0.22 to 8.04	0.751	-	-	-	1.32	0.21 to 8.14	0.766
	Borderline Personality Disorder	4.01	0.40 to 40.57	0.240	-	-	-	10.18	0.48 to 213.95	0.135
Substance abuse	Other personality disorder	3.05	0.41 to 22.93	0.278	2.53	0.30 to 21.14	0.390	-	-	-
Impulse control disorder	Other Psychoses	0.54	0.04 to 6.44	0.625	0.61	0.05 to 8.30	0.714	-	-	-
	Other personality disorder	11.54	0.92 to 143.32	0.057	8.63	0.47 to 158.37	0.147	-	-	-
Neurocognitive disorder	Schizophrenia	1.22	0.05 to 28.12	0.902	2.20	0.05 to 104.10	0.689	-	-	-
	Other Psychoses	0.24	0.03 to 2.08	0.197	-	-	-	0.67	0.05 to 8.65	0.756
	Other personality disorder	0.56	0.06 to 5.29	0.614	-	-	-	2.24	0.09 to 53.66	0.618
Sleep disorder	Bipolar disorder	2.94	0.20 to 44.15	0.435	-	-	-	-	-	-
	Depression	1.81	0.28 to 11.81	0.537	-	-	-	-	-	-
Pathological gambling disorder	Bipolar disorder	1.10	0.09 to 12.77	0.942	1.02	0.08 to 12.51	0.985	-	-	-

-; values omitted (p-value=1)
HR°: Hazard Ratio adjusted for sex and age; HR*: Hazard Ratio adjusted for age

developing depression was increased (HR 4.06, 95% IC 1.18 to 14.00, p=0.026).

Discussion

The study of comorbidity in psychiatry carries an important diagnostic role, since the possible overlapping of different symptoms, deriving from other mental diseases, could lead to confusing the traits of the main disease with those due to an ignored condition of comorbidity (Kessler, 1997; Maj, 2005). Furthermore, although not linked to causality relationships, the coexistence of different diseases can be held accountable for mutual worsening of symptoms, as well as insufficient therapeutic response and worse disease course (Charlson, Pompei, Ales, & MacKenzie, 1987; Hall, Lynskey, & Teesson, 2001; Wancata, Benda, Windhaber, & Nowotny, 2001). Understanding the reasons why two or more mental disorders frequently appear together as comorbid, could bring benefits through the detection of new and more efficient strategies, in terms of prevention and treatment, with a positive impact on patients' management and healthcare expenditure (Hochlehnert, Niehoff, Herzog, & Löwe, 2007; Wolff, Heister, Normann, & Kaier, 2018).

The present study is part of a research line that starts with the observation of high comorbidity rates among psychiatric disorders (Plana-Ripoll et al., 2019). The first attempts to organize these findings in an explanatory framework have examined the role of so-called "higher-order" psychopathological dimensions, inclusive of a series of disorders that shared the fundamental traits of the Internalizing (anxiety, depression), Externalizing (hyperactivity, conduct) and Psychotics (schizophrenia, bipolar disorders) (Kotov, Krueger, Watson, Achenbach, Althoff, Bagby, Brown et al., 2017). However, the research results showed that these dimensions are often overlapped and correlated with each other, suggesting the possible existence of a general factor of psychopathology, the "P factor", which could explain the variance between psychiatric symptoms and be predictive of different outcomes, including impairment of general and socio-occupational functioning (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017).

Our study showed that 54.4% of the sample presented at least one-lifetime psychiatric comorbidity, according to previous population studies reporting one or more lifetime diagnoses in 45-54% of individuals with a mental disorder (Bijl et al., 1998; Andrews et al., 2002; Jacobi et al., 2004; Kessler et al., 2012).

"Personality Disorders" (Borderline Personality Disorder + Other Personality Disorders) was the most comorbidity-associated diagnostic class in our sample, presenting more than 3 previous diagnoses in 51.5% of the cases; this finding concurs with studies in literature indicating comorbidity prevalence rates of 42% in Cluster A and 83% in Cluster B Personality Disorders (Lenzenweger, Lane, Loranger, & Kessler, 2007). These

clinical conditions are linked to higher recurrence rates, poor response or compliance to treatment, and a higher risk of suicidal behavior, representing a therapeutical challenge for mental health professionals.

Concerning diagnostic trajectories, in our sample heterotypic transition diagnostic patterns emerged substantially for all the onset diagnoses considered, except for the "Schizophrenia" category of whom 75% of the subjects have been receiving a psychotic-class diagnosis (Schizophrenia/Other psychotic disorders) lifetime. This data is in accordance with disorder features, representing Schizophrenia a stable diagnosis with the longest disease progression among other considered pathologies (Mean disease duration years = 24.20 ± 12.76) and, consequently, with a diagnostic homotypic evolutionary pattern. Moreover, a significantly higher risk to developing Schizophrenia and Borderline Personality Disorder emerged in patients who had Other psychotic disorder and Bipolar disorder as onset diagnosis, respectively. Finally, regarding gender differences, no significant differences emerged, except for women diagnosed with the onset of Bipolar disorders who presented a high risk of developing Borderline personality disorder.

The obtained results should be interpreted with extreme caution due to several limitations: first of all, the relatively small sample size does not allow to adequately evaluating comorbidity and diagnostic progression of some diagnostic classes (i.e OCD and Eating disorders). Another limitation is represented by the restricted recruitment area, so this may limit the generalizability and validity of the obtained results. Furthermore, the retrospective study design based on past clinical records can raise concern on the possible influence of diagnostic biases, as well as on the underestimation of lifetime prevalence of disorders considered.

Despite the limitations, the results of the study highlighted a tendency to make multiple diagnoses over psychiatric patients' lifetime in the majority of cases, often escaping from the original onset nosographic domain. More generally, our findings agree with a broad consensus that describes psychiatric symptomatic dimensions rather overlapped and correlated with each other, leading to a more transdiagnostic clinical approach.

Further studies on larger sample more representative of the general population and conducted with standardized and codified methods to collect the data on the categorical diagnoses are needed, in order to better define the important aspects of lifetime comorbidity and diagnostic trajectories of psychiatric disorders.

References

Andrews, G. (1996). Comorbidity and the general neurotic syndrome. *The British journal of psychiatry. Supplement*, (30), 76–84.

Andrews, G., Goldberg, D. P., Krueger, R. F., Carpenter, W. T., Hyman, S. E., Sachdev, P., & Pine, D. S. (2009). Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity? *Psychological Medicine*, *39*(12), 1993-200. https://doi.org/10.1017/S0033291709990250.

Andrews, G., Slade, T., & Issakidis, C. (2002). Deconstructing current comorbidity: data from the Australian National Survey of Mental Health and Well-Being. *Br J Psychiatry.;181*, 306-314. doi:10.1192/bjp.181.4.306.

Bijl, R. V., Ravelli, A., & van Zessen, G. (1998). Prevalence of psychiatric disorder in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Social Psychiatry and Psychiatric Epidemiology, 33*(12), 587–595.

Borsboom, D., Cramer, A. O., Schmittmann, V. D., Epskamp, S., & Waldorp, L. J. (2011). The small world of psychopathology. *PLoS One*, *6*(11):e27407. doi:10.1371/journal.pone.0027407.

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87).

Goldberg, J., & Fagin-Jones, S. (2004). Diagnosing and Treating Anxiety Comorbidity in Bipolar Disorders. *Psychiatr Ann.*, 34, 874-884. doi: 10.3928/0048-5713-20041101-16.

Hall, W. D., Lynskey, M. T., & Teesson, M. (2001). "What is comorbidity and why does it matter?". *National Comorbidity Project, edn. 1, Commonwealth of Australia, Canberra*, 11-17.

Hochlehnert, A., Niehoff, D., Herzog, W., & Löwe, B. (2007). Höhere Kosten bei internistischen Krankenhauspatienten mit psychischer Komorbidität: Fehlende Abbildung im DRG-System [Elevated costs of treatment in medical inpatients with psychiatric comorbididity are not reflected in the German DRG-system]. *Psychotherapie, Psychosomatik, medizinische Psychologie*, *57*(2), 70–75. https://doi.org/10.1055/s-2006-951924.

Jacobi, F., Wittchen, H. U., Hölting, C., Höfler, M., Pfister, H., & Lieb, R. (2004). Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health Interview and Examination Survey (GHS). *Psychological Medicine, 34*(4), 597–611. https://doi.org/10.1017/S0033291703001399.

Kendell, R., & Jablensky, A. (2003). Distinguishing between the validity and utility of psychiatric diagnoses. *The American journal of psychiatry*, *160*(1), 4–12. https://doi.org/10.1176/appi.ajp.160.1.4.

Kessler, R. C. (1997). The prevalence of psychiatric comorbidity. In S. Wetzler & W. C. Sanderson (Eds.). *An Einstein psychiatry publication, No. 14. Treatment strategies for patients with psychiatric comorbidity*, 23–48. John Wiley & Sons Inc.

Kessler, R. C., Avenevoli, S., & McLaughlin, K. A. (2012). Lifetime co-morbidity of DSM-IV disorders in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). *Psychol Med., 42*(9), 1997-2010. https://doi.org/10.1017/S0033291712000.

Klerman, G. L. (1990). Approaches to the phenomena of comorbidity. *Comorbidity of mood and anxiety disorders*, 13–37.

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., . . . Zimmerman, M. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of abnormal psychology*, *126*(4), 454–477. https://doi.org/10.1037/abn0000258.

Kraemer, H. C., Shrout, P. E., & Rubio-Stipec, M. (2007). Developing the diagnostic and statistical manual V: what will "statistical" mean in DSM-V? *Social psychiatry and psychiatric epidemiology*, *42*(4), 259–267. https://doi.org/10.1007/s00127-007-0163-6.

Lahey, B. B., Krueger, R. F., Rathouz, P. J., Waldman, I. D., & Zald, D. H. (2017). A hierarchical causal taxonomy of psychopathology across the life span. *Psychological bulletin*, *143*(2), 142–186. https://doi.org/10.1037/bul0000069.

Lenzenweger, M. F., Lane, M. C., Loranger, A. W., & Kessler, R. C. (2007). DSM-IV personality disorders in the National Comorbidity Survey Replication. *Biological psychiatry*, *62*(6), 553–564. https://doi.org/10.1016/j.

biopsych.2006.09.019.
Maj, M. (2005). "Psychiatric comorbidity": an artefact of current diagnostic systems? *The British journal of psychiatry : the journal of mental science*, 186, 182–184. https://doi.org/10.1192/bjp.186.3.182.
Plana-Ripoll, O., Pedersen, C. B., Holtz, Y., Benros, M. E., Dalsgaard, S., De Jonge, P., & Gunn, J. (2019). Exploring comorbidity within mental disorders among a Danish national population. *JAMA psychiatry, 76*(3), 259-270.
Schoevers, R. A., Deeg, D. J., van Tilburg, W., & Beekman, A. T. (2005). Depression and generalized anxiety disorder: co-occurrence and longitudinal patterns in elderly patients. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*, *13*(1), 31–39. https://doi.org/10.1176/appi.ajgp.13.1.31.
Spoorthy, M. S., Chakrabarti, S., & Grover, S. (2019). Comorbidity of bipolar and anxiety disorders: An overview of trends in research. *World journal of psychiatry*, *9*(1), 7–29. https://doi.org/10.5498/wjp.v9.i1.7.
Strakowski, S. M., Keck, P. E., McElroy, S. L., Lonczak, H. S., & West, S. A. (1995). Chronology of comorbid and principal syndromes in first-episode psychosis. *Comprehensive psychiatry, 36*(2), 106–112 https://doi.org/10.1016/s0010-440x(95)90104-3.
Wancata, J., Benda, N., Windhaber, J., & Nowotny, M. (2001). Does psychiatric comorbidity increase the length of stay in general hospitals? *General hospital psychiatry*, *23*(1), 8–14. https://doi.org/10.1016/s0163-8343(00)00110-9.
Wolff, J., Heister, T., Normann, C., & Kaier, K. (2018). Hospital costs associated with psychiatric comorbidities: a retrospective study. *BMC health services research*, *18*(1), 67. https://doi.org/10.1186/s12913-018-2892-5.