Schizophrenia today: epidemiology, diagnosis, course and models of care

La schizofrenia oggi: epidemiologia, diagnosi, decorso e modelli di cura

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Summary

Schizophrenia is a serious public health problem: according to WHO it is responsible for 1.1% of total disability adjusted life years (DALYs) and absorbs 1.5-3.0% of all healthcare expenditure in developed countries. In Europe, it is estimated that there are about 5 million persons with schizophrenia, with a prevalence of 0.6-0.8%. In 98% of cases onset occurs before the age of 40 years with a slight male predominance. Several environmental factors have been implicated in the genesis of schizophrenia. Epidemiological data in Italy are less accurate than those in other Western countries. The article presents national and regional epidemiological data on the characteristics of healthcare in patients with schizophrenia. The mortality rate of schizophrenic patients is approximately double that of the general population. The main causes of death are suicide, cardiovascular disease and cancer. The DSM-5 has made important changes to the diagnostic criteria of schizophrenia compared with the previous edition, eliminating the priority assigned to first-rank symptoms as well as diagnostic subtypes, and introducing the use of psychopathological dimensions in an attempt to favour a dimensional approach to diagnosis. In order to increase the reliability of differential diagnosis of schizoaffective disorder, in the DSM-5 the diagnostic criteria for this disorder are more strictly defined. A prodromal phase of schizophrenia can be demonstrated in about 75% of patients with a first psychotic episode. This initial phase lasts an average of five years, has a pathological significance and often leads to psychosocial deficits. Only 18% of patients show an acute onset of disease with symptoms that appear within a month, while 68% have an insidious onset with early symptoms appearing for over a year before the first hospitalisation. It has been shown that the duration of untreated psychosis is negatively associated with the symptomatic and functional long-term outcomes of schizophrenia. It is therefore believed that the interventions implemented during the early stages of the disease, reducing the duration of untreated psychosis and/or addressing the functional deterioration that occurs before the first psychotic episode may help to preserve the overall functional capacity of the individual.

More than 30 years after the approval of the 180/78 Law and creation of a community mental health system, the Italian network of community services for mental health care likely represents a model to be followed in other countries. In the past 10 years, numerous national and regional studies have evaluated the efficiency of the community mental health system in diagnosis and care of patients with schizophrenia. Overall, the Italian mental health system is quite efficient, but much remains to be done. In particular, a national and regional computerised information system is urgently needed, which does not exist in several regions. In addition, the willingness to implement innovative programmes integrated with routine activities of community services can improve the quality and promptness of care by reducing the duration of untreated psychosis and therefore the deterioration of social functioning of affected individuals.

Key words

Schizophrenia • Psychotic disorders • Community Mental Health Services

Epidemiology

Prevalence: primary international data

Schizophrenia is a ubiquitous disease, present in all cultures and historical periods, even if its manifestations have likely changed over time [1]. Schizophrenia is a major burden for healthcare: a large international project promoted by the World Health Organization (WHO) reported that schizophrenia is responsible for 1.1% of the total disability adjusted life years (DALYs) and 2.8% of the years lived with disability (YLDs) [2]. More recent data from the *Global Burden of Diseases, Injuries, and Risk Factors Study 2010* [3] indicated that mental disorders and substance abuse accounted for 183.9 million DALYs, or 7.4% of all DALYs worldwide in 2010. Moreover, they represent the primary cause of YLDs globally. Among mental disorders, schizophrenia is responsible for 7.4% of DALYs and YLDs, and 7.1% of years of life lost to premature mortality (YLLs). In reality, schizophrenia is responsible for 1.5-3.0% of healthcare expenses in developed countries [4]; in Italy, it has been estimated that the annual cost of care of a patient with schizophrenia is around € 25,000, of which 30% are direct costs, and 70% are indirect costs [5].

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The available data regarding the social impact of schizophrenia in Europe are similar to those in the rest of Western countries. In a recent epidemiologic study on the entity and burden of mental disorders in Europe carried out in 2010 [6], it was estimated that each year 38.2% of the European population suffers from a mental disorder. There were about 5 million subjects affected by a psychotic disturbance (including schizophrenia) or about 1.2% of the population, which was increased relative to data from 2005 (3.7 million, 0.8%). The social costs of social costs of psychiatric and neurologic disabilities are very high, and estimated to be 30.1% of the total disease burden in women and 23.4% in men (26.6% overall); it has been estimated that the social costs of schizophrenia amount to about 640,000 DALYs.

International epidemiologic studies have indicated that the disease has an incidence that varies from 0.11 to 0.69 per 1000, while the prevalence is estimated to be from 0.6 to 0.8% [1]. In 98% of cases, the disease appears before the age of 40 years [7], and in fact, development under the age of 45 years was considered as diagnostic criterion in the DSM-III for a diagnosis of schizophrenia.

While some studies have indicated that there is no gender preference for schizophrenia, others have reported that it is more prevalent in men (1.4:1), especially in cases of juvenile onset [8] (Table I). Patients with schizophrenia are more often nubile compared with the general population as demonstrated in a recent study from Australia [9]. Moreover, in metropolitan areas and among immigrants, the incidence of the disease appears to be greater than in rural areas and among natives [10]. Schizophrenia is also more frequent in lower socio-economic classes and in those with lower levels of education. This may be related to a phenomenon known as downdrift in which schizophrenia leads to lower levels of social achievement and levels of employment [11].

Regarding environmental factors at the pathogenesis of schizophrenia [12], in addition to differences in prevalence and incidence depending on the urban or rural area, neighbourhood, immigration status and season of birth, several other risk factors have been implicated in foetal and perinatal life. These include infections (e.g. measles, influenza, toxoplasma, type 3 herpes simplex virus), nutritional deficiencies (e.g. malnutrition, folic acid, iron, or vitamin D deficit), paternal age, foetal/neonatal hypoxia and obstetric complications. Other potential determining factors of neurological development, including cannabis, socio-economic status, trauma and infections during infancy and adolescence, have been implicated.

The role of the social environment in the development of schizophrenia and other psychotic disturbances has been intensely studied in recent years [13 14]. One particularly interesting aspect is the association between urban life (and social exclusion) and incidence of schizophrenia. Several studies have shown that urban life is associated with a higher incidence of schizophrenia and non-affective psychoses. Moreover, substantial variation in the incidence of these disturbances has been observed depending on the neighbourhood of residence. The results of studies that have investigated the relationship between urban life and schizophrenia have suggested that it is improbable that this could completely explain the observed geographic variations in the incidence of schizophrenia. The available evidence suggests that the impact of negative social context (such as population density, fragmentation and social deprivation) on the risk of psychosis can be explained or modified by the individual level of environmental exposure (use of cannabis, adversity, social exclusion, or discrimination).

Some recent models of psychosis have implicated that stressful events may have a role in the development of schizophrenia. These include not only those occurring during infant life, but also those at an adult age. How-

TABLE I.
Influence of sex, migrant status, urban status, secular trend, economic status and latitude on the distribution of estimates from the systematic reviews of schizophrenia incidence, prevalence and mortality (from McGrath et al., 2008, modified) [1]. *Influenza del sesso, dello stato di migrante, dello stato di urbanizzazione, dello stato economico e della latitudine sulla distribuzione delle stime su incidenza, prevalenza e mortalità della schizofrenia negli studi epidemiologici (da McGrath et al., 2008, mod.)* [1].

	Sex	Migrant status	Urban status	Secular trend	Economic status	Latitude
Incidence: core	Males > females	Migrant > native born	Urban > mixed urban and rural	Falling over time	No significant difference	High latitude > lower latitude (males only)
Prevalence: combined estimates	Males = females	Migrant > native born	No significant difference	Stable	Developed > least developed	High latitude > lower latitude
Standardised mortality ratio: all-cause	Males = females	Not available	Not available	Rising over time	No significant difference	Not available

ever, the available studies examining exposure to stressful events in an adult age may generally be considered to have poor methodology, and at the present it is not possible to reach any definitive conclusions [15].

Concerning demographic data in Europe, in a study carried out in 4 countries (Germany, Greece, Italy and Spain) on 4000 patients with schizophrenia [16], the demographic characteristics of patients is relatively homogeneous, with the exception of Germany in which patients tended to be judged by their psychiatrist as more severe (59.0% *vs*. 35.9% in Greece and 44.5% in Italy), have a higher level of hospitalisation (49.3% *vs*. 15.0% in Greece and 44.9% in Italy) even during the long-term (27.4% *vs*. 17% in Italy), to live alone more frequently instead of in a family context (46.7% *vs*. < 20% in other countries) and to prepare meals alone (90% *vs*. 64% in Italy).

Prevalence: Italian data

No data is available on the prevalence and incidence of schizophrenia in Italy. The reasons for this are two-fold. The first is that the expected prevalence (based on studies in other countries and several small regional studies in Italy) is about 4–5 per 1000, although studies are needed on a much larger population (at least 50,000 individuals) in order to have a more accurate estimate with an acceptable confidence interval. The second reason is that schizophrenia, unlike other mental health disorders such as most anxiety disorders and unipolar depression (assessed in the ESEMED study [*European Study of the Epidemiology of Mental Disorders*], the only epidemiological study of mental disorders carried out in the general population in Italy), cannot be considered reliable as it was performed using non-professional interviewers (with low associated costs); to involve professionals would have been cost prohibitive [17].

Based on international data, in Italy, with an adult population (age ≥ 18 years) of about 49 million individuals, it can be estimated that there are around 245,000 people with or who have been affected with a schizophrenic disorder at some point in their lifetime [18].

Data from the SEME project (Sorveglianza Epidemiologica integrata in salute Mentale), which has the objective of monitoring based on a network of centres throughout Italy, has indicated that psychotic disorders (DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder and delirium disorders) have an incidence of 7.4 cases per 100,000 inhabitants [19]. Of these, 17.5% have an age between 14-25 years, 25.2% between 26-35 years, 28.0% from 36-45 years, 17.5% from 46-55 years, 5.6% between 56-65 years and 6.3% have an age ≥ 66 years.

In the PROGRES study (PROGetto RESidenze), sponsored by the Italian National Institutes of Health in 2000 with the objective of studying all non-hospital residential structures present in Italy, a battery of standardised instruments were used to study a casual sample of 20% of the these (267 of 1370 structures) and patients housed within (for a total of 3005) in depth. In particular, data from 2004 on 1577 patients in 166 structures [20] indicated that 565 patients were affected by schizophrenia and related psychoses, or 37.9% of the guests in public structures and 25.9% of private structures; this corresponds to 33.4% of the voluntary admissions and to 53.1% of obligatory treatments [21]. In this group, 75.1% of patients with schizophrenia were treated during the preceding month in a public mental health centre, 6.5% in a university hospital structure, and 1.8% in a SERT (service for substance abuse). Among the contributing factors for admission of patients with schizophrenia, 66.5% had employment and/or social issues, 56.3% needed reassessment of pharmacological therapy, 43.3% had conflicts with family and 34.7% with other persons, 19.3% had violent behaviour towards others and 9.1% towards objects, and 6.4 had attempted suicide.

Concerning data on hospitalisation of individuals with schizophrenia in Italy [22] (Table II), the national mean was 77.58 per 100,000 inhabitants, with notable differences between regions (range 25.6-144.4) (Istat, 2008). The lack of significant epidemiological data that can justify a greater need for hospital care for the regions with a higher standardised incidence is probably related to the different allocations between hospital and local healthcare services.

In Italy, regional epidemiologic data are derived from regional databases; of these, the systems in Lombardia, Friuli-Venezia Giulia (diagnosis missing in 40% of new cases), Liguria (not completely computerised and online), Emilia Romagna (diagnosis missing in 40% of new cases) and Lazio are available. A study by Lora et al. [23] carried out in Lombardia using the data present in the regional database identified 44,462 residents in the region with an age >18 years who had a diagnosis of schizophrenic spectrum or affective disorders that were treated in 2007 in a mental health department: the demographic characteristics of these patients are shown in Table III. It is interesting to note that only about half of this population (in particular, only 49.3% of those with schizophrenia) received minimal adequate treatment.

Additional data on the Lombardia region [24] indicate that the prevalence of subjects with schizophrenia in 2009 who had at least one contact with mental health services was 14.6 cases per 1000 inhabitants > 17 years of age. The incidence of schizophrenic disorders in 2009 was 2.2 cases per 10,000 inhabitants over >17 years of age with a prevalence of 37.9 cases per 10.000 inhabitants over the age of >17 years (Tables IV, V).

Continuity of care was guaranteed in 57% (21.2 subjects per 10,000 inhabitants) of patients with schizophrenic

TABLE II.
Hospital discharges with a diagnosis of schizophrenia and related disorders in 2008 (Data from Istat) (from Brenna and Di Novi, modified)[22]. *Dimissioni ospedaliere per diagnosi di schizofrenia e disturbi correlati - anno 2008 (Fonte: elaborazioni dati Istat) (da Brenna e Di Novi, mod.)* [22].

Region	Discharges	Raw rate per 100,000 inhabitants	Standardised rate per 100,000 inhabitants	% of total discharges with psychic disorders	Mean hospitalisation time
	Schizophrenia and related disorders*				
Piemonte	3,947	89.36	88.83	18.65	22.49
Valle d'Aosta	135	106.70	108.40	16.90	15.25
Lombardia	7,652	78.95	78.13	17.03	16.35
Trentino-Alto Adige	673	66.44	66.10	10.51	17.65
Veneto	3,071	64.36	62.69	14.03	19.65
Friuli-Venezia Giulia	320	26.09	25.56	8.96	15.56
Liguria	1,998	123.91	127.72	16.35	13.91
Emilia-Romagna	2,796	64.92	65.33	14.06	17.77
Toscana	1,786	48.37	50.17	11.94	13.58
Umbria	420	47.23	49.02	13.28	15.78
Marche	1,352	86.59	87.15	19.88	19.82
Lazio	4,231	75.64	75.15	12.31	11.57
Abruzzo	1,125	84.63	85.59	13.72	14.14
Molise	278	86.65	88.59	16.11	14.93
Campania	4,221	72.62	73.01	19.52	30.70
Puglia	2,711	66.48	66.52	16.70	14.24
Basilicata	324	54.84	55.82	11.28	13.10
Calabria	2,086	103.87	105.80	20.92	36.02
Sicilia	7,106	141.17	144.40	24.15	12.23
Sardegna	1,093	65.52	66.07	14.15	13.44
North	20,592	71.55	71.22	15.73	18.07
Centre	7,789	66.36	67.11	13.14	13.75
South	18,944	90.90	91.32	19.37	19.71
Italy	47,701	77.74	77.58	16.39	18.04

* ICD-9 classification, aggregated clinical codes (ACC) 070: schizophrenia and related disorders.

disorders in 2009: for 27% with a *Clinical package* (patients cared for only at psycho-social centres and only by professional clinical care providers, i.e. psychiatrists and psychologists), 43% with a *Community package* (patients receiving care at psycho-social centres, but in addition to contact with clinicians, had contact with other professional healthcare providers such as nurses, social workers and rehabilitations therapists), 8% with a *Day care package* (patients received treatment in daily centres without being admitted to Psychiatric Services or residential structures), 12% with a *Hospital package* (in at least on occasion, patients are admitted to a SPDC without being hosted in a residential structure) and 10% with a *Residential package* (patients had at least one experience in a residential structure).

Concerning data from the psychiatric database in the Lazio region, in 2011, of a total of 33,057 discharges with a primary psychiatric diagnosis (ICD9-CM codes between 290 and 319), of which 55.4% referred to ordinary hospitalisations and 44.6% in day hospital, 25.4% of those in ordinary hospitalisation and 2.9% of those in day hospital had a primary diagnosis of schizophrenia or paranoid state [25]. Considering ordinary hospitalisations with a primary diagnosis of schizophrenia or paranoid

TABLE III.
Baseline characteristics of patients with severe mental illness and predictors of receipt of minimally adequate treatment at 12 months (from Lora et al., 2011, modified) [23]. *Caratteristiche basali dei pazienti con malattia mentale grave e fattori predittivi di un trattamento minimamente adeguato a 12 mesi (da Lora et al., 2011, mod.)* [23].

	Baseline (n = 44,462)		Minimally adequate treatment at 12 month (n = 21,658)			
Characteristic	**N**	**%**	**N**	**%[a]**	**Relative risk**	**95 % CI**
Clinical and sociodemographic						
Age						
18-29[b]	3,710	8.3	1,956	52.7	1,00	
30-44	13,859	31.2	7,378	53.2	1.02	0.99-1.06
45-59	14,598	32.8	7,281	49.9	1.01	0.98-1.04
≥ 60	12,295	27.7	5,043	41.0	0.86*	0.83-0.90
Gender						
Female[b]	25,016	56.3	11,728	46.9	1.00	
Male	19,446	43.7	9,930	51.1	1.03*	1.01-1.05
Education (year)						
≥ 14[b]	2,059	4.6	997	48.4	1.00	
9-13	10,853	24.4	5,685	52.4	1.06*	1.02-1.11
6-8	18,879	42.5	9,618	51.0	1.04	1.00-1.09
1-5	12,671	28.5	5,358	42.3	0.97	0.92-1.02
Employment						
Unemployed[b]	28,963	65.1	14,041	48.5	1.00	
Employed	15,499	34.9	7,617	49.2	0.94*	0.93-0.96
Marital status						
Married[b]	18,190	40.9	8,535	46.9	1.00	
Never married	19,447	43.8	10,116	51.9	1.03*	1.01-1.06
Divorced or separated	3,984	9.0	1,906	47.8	1.02	0.99-1.05
Widowed	2,811	6.3	1,101	39.2	0.95*	0.90-0.99
Urbanicity						
Low[b]	3,461	7.8	1,669	48.2	1.00	
Medium	12,296	27.7	5,867	47.7	0.99	0.95-1.03
High	28,705	64.6	14,122	49.2	1.01	0.97-1.06
Charlson Comorbidity Index[c]						
0[b]	40,448	91.1	19,887	49.1	1.00	
1	1,577	3.6	738	46.8	1.01	0.97-1.06
≥ 2	2,397	5.4	1,033	43.1	0.95*	0.91-0.99
Type of disorder						
Mayor depressive disorder[b]	16,281	36.6	7,408	45.5	1.00	
Bipolar disorder	5,711	12.8	3,179	55.7	1.14*	1.11-1.18
Schizophrenia	22,470	50.5	11,071	49.3	1.08*	1.06-1.10
Type of care						
Continuous[b]	26,349	59.3	15,663	59.4	1.00	
Former	12,563	28.3	3,682	29.3	0.50*	0.48-0.51

(continues)

TABLE III. *(continued).*

	Baseline (n = 44,462)		Minimally adequate treatment at 12 month (n = 21,658)		Relative risk	95 % IC
Characteristic	N	%	N	%[a]		
Clinical and sociodemographic						
Type of care						
New (treatment at index date)	5,550	12.5	2,313	41.7	0.74*	0.72-0.76
Environmental (Department of Mental Health)						
Psychiatric beds (per 10,000 population)						
0.93-2.48[b]	11,449	25.8	5,307	46.4	1.00	
2.49-3.22	11,019	24.8	5,218	47.4	0.96	0.85-1.08
3.23-4.47	11,100	25.0	5,763	51.9	1.09	0.96-1.24
4.48-17.58	10,894	24.5	5,370	49.3	1.01	0.90-1.14
Hours worked in community mental health facilities (per 10,000 population)						
812-2,180	11,590	26.1	5,611	48.4	1.00	
2,181-2,660	10,525	23.7	5,027	47.8	1.05	0.92-1.19
2,661-3,122	11,765	26.5	5,792	49.2	1.04	0.92-1.18
3,123-6,791	10,582	23.8	5,228	49.4	1.06	0.94-1.20

[a] Preferences are based on the N for each characteristics at baseline (i.e., the row percentage); [b] Reference; [c] Higher scores indicate more comorbidity; * $p < 0.05$.

state, about 45% of recoveries were in public hospitals, 20% were in university psychiatric departments and less than 35% in certified neuropsychiatric structures. Day hospital discharges with a primary diagnosis of schizophrenic disorders represented 17.3% of day hospital admissions with a primary psychiatric diagnosis (about 38% of admissions to day hospital and 8% of admission to university day hospitals). Among emergency admissions with a primary psychiatric diagnosis in individuals >14 years of age, about 2% had a primary diagnosis of schizophrenia or paranoid state.

Data from the epidemiological database in the Veneto region [26] indicate that the prevalence of psychiatric patients receiving care in hospitals or in satellite centres is 17.2 cases per 1000 inhabitants over the age of >17 years (of which 58% are female). Moreover, 82.6% of patients received care only in satellite care centres and 7.7% only hospital care, while 9.7% received both. Among patients receiving care in satellite centres, 23% had a diagnosis of schizophrenia, with a prevalence of 2.1 cases per 1000 inhabitants. Among those receiving hospital care, 22% were affected by schizophrenia, with the majority (87%) receiving care in public hospitals. Considering the ambulatory and non-ambulatory care received in patients with schizophrenia or functional psychoses, 29.8% consisted of interview, 22.6% of psychiatric somatotherapy (coded with DRG 942, otherwise known as "physical therapy in psychiatry": this includes the subcodes for narcoanalysis, chemical shock therapy, electroshock therapy, lithium therapy, neuroleptic therapy, etc.), 14.2% were follow-up visits, 8.4% were therapeutic interventions and 8.2% were related to the patient's employment. In addition, 57% of the days spent in semi-residential structures and 64% of those in residential structures were related to clients with schizophrenia and other functional psychoses. Considering discharges in subjects >17 years of age with a psychiatric pathology, 22% (37.6% of those discharged from public hospitals) had a diagnosis of schizophrenia and other functional psychoses, and were hospitalised for a mean of 19.1 days (median 14.0 days). In 2009, 58.4% of mandatory hospitalisations were attributed to a diagnosis of schizophrenia and other functional psychoses.

In Toscana, in 2011, regional psychiatric services were caring for 2507 patients with schizophrenia and related disorders, or 8.7% of all patients under their care [27]; it should however be considered that a diagnosis was not available or missing in 40.5% of patients, and thus the above incidence is undoubtedly underestimated.

Mortality associated with schizophrenia

In a systemic review of 37 studies that provided data on standardised rates of mortality [28], the standardised

TABLES IV-V.
Incidence and prevalence of mental disorders in Lombardia from 1999 to 2009 (from Lora et al., 2012, modified) [24]. *Incidenza e prevalenza trattata delle malattie mentali in Lombardia dal 1999 al 2009 (da Lora et al., 2012, mod.)* [24].

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Males											
Total	21	25	28	28	27	26	20	26	27	29	32
Age 18-24 years	39	43	45	45	44	40	27	37	40	41	45
Age 25-34 years	24	29	34	33	33	31	23	29	30	33	32
Age 35-44 years	19	24	28	29	28	27	22	28	29	29	32
Age 45-54 years	16	20	24	24	23	24	19	25	26	29	33
Age 55-64 years	14	17	19	19	19	19	16	21	22	22	27
Age > 64 years	20	22	24	23	23	22	17	23	21	24	27
Females											
Total	26	32	36	36	34	34	28	37	37	38	40
Age 18-24 years	34	42	51	52	46	43	39	49	51	50	58
Age 25-34 years	30	37	41	42	41	40	44	46	45	46	45
Age 35-44 years	28	34	39	41	39	40	32	42	41	44	46
Age 45-54 years	24	30	32	34	31	33	29	37	37	39	42
Age 55-64 years	21	25	28	29	26	27	23	31	32	31	33
Age > 64 years	24	30	32	30	28	27	22	28	28	30	32
Diagnostic groups											
Schizophrenic disorders	2.5	2.5	2.5	2.4	2.4	2.7	2.2	2.4	2.3	2.3	2.2
Affective disorders	5.5	6.7	7.4	7.3	6.7	7.3	6.2	7.3	7.1	7.5	8.0
Neurotic disorders	7.1	9.8	11.2	11.4	10.7	10.9	9.4	12.1	12.4	13.0	14.4
Personality disorders	2.1	2.4	2.6	2.5	2.3	2.2	1.7	2.2	2.2	2.2	2.3

Rates per 10,000 population 18 and over.

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Males											
Total	100	109	120	125	129	131	132	132	133	139	147
Age 18-24 years	102	106	112	110	110	109	101	98	98	100	105
Age 25-34 years	112	121	134	140	142	141	139	137	141	140	139
Age 35-44 years	113	122	138	146	150	152	155	154	153	162	169
Age 45-54 years	103	113	129	135	140	146	151	156	154	166	182
Age 55-64 years	86	97	105	110	114	120	123	128	130	139	153
Age > 64 years	76	85	95	97	101	102	103	101	101	105	112
Females											
Total	119	132	145	154	156	160	163	166	166	171	178
Age 18-24 years	84	94	108	116	109	110	112	112	112	109	119
Age 25-34 years	108	118	131	138	140	141	142	145	148	142	140
Age 35-44 years	135	147	163	170	173	178	180	182	181	185	190
Age 45-54 years	137	142	168	179	183	192	198	205	201	213	228
Age 55-64 years	136	147	160	172	174	180	185	193	194	205	212
Age > 64 years	107	121	131	137	140	142	144	144	144	151	158
Diagnostic groups											
Schizophrenic disorders	29.6	31.1	32.6	33.4	34.4	35.1	35.9	36.1	35.8	36.8	37.9
Affective disorders	25.2	28.9	32.3	34.3	34.7	36.5	37.1	38.0	37.7	40.0	42.2
Neurotic disorders	22.3	26.9	31.3	33.2	33.4	35.4	35.8	37.0	36.7	39.4	42.4
Personality disorders	10.5	11.7	13.0	13.3	13.4	13.6	13.7	14.0	13.9	14.3	15.0

Rates per 10,000 population 18 and over.

all-cause mortality rate was 2.58 (10-90% quantile, 1.18-5.76), with no difference between gender. In particular, death by suicide was 12 times higher than in the general population, but even mortality due to natural causes was higher in patients with schizophrenia (Table VI).

A successive meta-analysis on retrospective epidemiological studies published in the preceding 4 years [29] revealed that the principal cause of death in patients with schizophrenia was suicide, cardiovascular disease and cancer. The cause of death was dependent on age, duration of follow-up and type of study. Treatment with antipsychotics appeared to reduce mortality compared with no treatment and treatment with atypical antipsychotics. These latter have been suspected to increase mortality as they may be associated with weight gain and worsening of metabolic parameters, although they did not appear to correlate with mortality and cardiovascular morbidity.

Another meta-analysis [30] confirmed the excess mortality in schizophrenic patients compared with the general population. At first diagnosis the prevalence of diabetes is only moderately increased, even if alterations in lipid metabolism, overweight and arterial hypertension are frequent; drug and alcohol abuse are common, as well as cigarette smoking and low levels of physical activity. During the first year of treatment with antipsychotics a significant increase in diabetes, obesity, lipid alterations and hypertension, with no change in the level of physical activity, smoking or drug/alcohol abuse, is observed. The authors concluded that the excess mortality for cardiovascular causes and cancer in patients with schizophrenia is at least in part related to the availability and quality of healthcare.

In another study [31] that investigated mortality trends for schizophrenia in death certificates in the United States that mention multiple causes of death from 1999 to 2010, mortality per 100,00 inhabitants decreased by 0.16%, from 1.58 in 1999 (3407 deaths) to 1.32 in 2010 (3422 deaths). The reduction was greater in women than men, and in whites than blacks. It also decreased in the Midwest and South, but not in Western states. In reality, mortality was increased in the age range 15-64 years (+28%), especially in males, and was decreased in those with an age ≥ 65 years (-35%). In subjects 15-64 years old, the increase was due to endocrine-metabolic causes (mostly diabetes mellitus), and to a lesser degree to cardiovascular causes, external causes (accidents, suicide, etc.) and cancer. It has recently been hypothesised that one of the reasons why subjects with schizophrenia tend to die earlier is that an advanced aging process related to the disease takes place [32].

Another aspect that warrants mention is the notable risk of death by suicide in patients with schizophrenia. In addition to the data mentioned above, it should be highlighted that the entity of risk depends firstly on the age of the population studied [33 34]: a Swedish study reported that the standardised mortality rate was 102.7 in young males, and 175.6 in young females [35]. Another study [36] documented that the standardised mortality rates showed considerable variation depending on the age of subjects, which ranged from 10.1 (6.6-18.2) in elderly patients, 52.2 (40.2-84.1) in middle-aged subjects and 94.5 (82.1-185.5) in the age range from 14-40 years.

A recent meta-analysis [37] showed that young age, male gender and higher level of education were risk factors for suicide; among factors related to the disease, in addition to previous suicide attempts, depressive symptoms, hallucinations, delirium and the presence of insight were also predictive factors. Even family history of suicide and substance abuse were associated with an increased risk of suicide.

An international study in 11 countries as part of the International Suicide Prevention Trial (InterSePT) evaluated the relation between transcultural differences and an effective suicide attempt in patients with schizophrenia and schizoaffective disorder [38]. In all geographic groups, history of alcohol and substance abuse and regular smoking status were associated with increased risk of suicide attempts. Male gender was more frequent in patients who attempted suicide alone in the European and North American cohorts. The only variables that differed significantly between geographic groups was age at first suicide attempt (lower in North America) and the number of suicide attempts (higher in North America).

Regarding data from Italy, in a retrospective study of 103 patients with a diagnosis of chronic schizophrenia or schizoaffective disorder who were followed as outpatients at the IRCCS Fatebenefratelli Centro San Giovanni di Dio in Brescia, those with a history of suicide attempt had a greater prevalence of abuse or dependence on nicotine (OR 3.4, $p < 0.05$), current or past depressive episodes (OR 6.5, $p < 0.002$), duration of untreated psychosis ≥ 1 year (OR 12.5, $p < 0.02$) and treatment with typical antipsychotics (OR 6.5, $p < 0.05$) [39].

Many studies have demonstrated that treatment with typical antipsychotics does not decrease the risk of suicide in patients with schizophrenia; among the second-generation antipsychotics, several investigations have suggested that clozapine can have beneficial effects in reducing the risk of suicide. In particular, InterSePT, a multicentre, international, randomised study that compared the efficacy of clozapine and olanzapine on suicidal behaviour in patients considered at high risk for suicide based on previous attempts or the presence of suicidal ideation demonstrated that clozapine was associated with a reduced suicidal behaviour (HR 0.76, 95% CI 0.58-0.97, $p = 0.03$) and suicide attempts (34 *vs*. 55, $p < 0.03$) compared with olanzapine [40]. Based on this, the FDA granted approval for clozapine for reduction of recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorder.

TABLE VI.
Standardised percentages of mortality for schizophrenia (from Saha et al., 2007, modified) [28]. *Percentuali standardizzate di mortalità per schizofrenia (da Saha et al., 2007, mod.)* [28].

		Quantile						
Causes of death	**No. of SMRs**	**10%**	**25%**	**Median**	**75%**	**90%**	**Mean (SD)**	**Geometric mean**
All-cause and middle-level categories								
All-cause (ICD-9 codes 001-799/E800-E999)	38	1.18	1-87	2.58	3.64	5.76	2.98 (1.175)	2.68
All-natural cause (ICD-9 codes 001-799)	6	0.69	1.04	2.41	2.90	4.10	2.31 (1.18)	2.03
All- unnatural cause (ICD-9 codes E800-E999)	3	5.56	5.56	7.50	12.73	12.73	8.60 (3.71)	8.10
Natural causes, cause specific								
Cardiovascular diseases (ICD-9 codes 390-429)	7	1.11	1.40	1.79	2.49	3.60	2.01 (0.83)	1.88
Cerebrovascular diseases (ICD-9 codes 430-438)	3	0.61	0.61	0.69	1.30	1.30	0.87 (0.88)	0.82
Digestive diseases (ICD-9 codes 520-579)	5	1.79	2.24	2.38	2.50	17.50	5.28 (6.84)	3.34
Endocrine diseases (ICD-9 codes 250-259)	3	2.20	2.20	2.63	11.66	11.66	5.50 (5.34)	4.07
Infectious diseases (ICD-9 codes 001-139)	3	1.60	1.60	4.29	7.80	7.80	4.56 (3.11)	3.77
Genitourinary diseases (ICD-9 codes 580-629)	3	1.54	1.54	3.70	4.29	4.29	3.18 (1.45)	2.90
Neoplastic diseases (ICD-9 codes 140-239)	7	0.71	1.00	1.37	2.01	2.40	1.44 (0.60)	1.33
Nervous diseases (ICD-9 codes 345-349)	4	1.60	1.95	4.22	6.57	7.00	4.26 (2.70)	3.55
Respiratory diseases (ICD-9 codes 460-519)	6	2.20	2.39	3.90	3.80	9.30	4.00 (2.66)	3.51
Other diseases (ICD-9 codes 1-389/630/799)	3	1.45	1.45	2.00	3.40	3.40	2.28 (1.01)	2.14
Unnatural causes, cause specific								
Accident (ICD-9 codes E800-E949)	6	1.20	1.63	1.73	5.10	8.40	3.30 (2.88)	2.51
Suicide (ICD-9 codes E950-E959)	10	0.66	5.90	12.86	21.43	174.25	43.47 (95.11)	16.13

ICD-9: International Classification of Diseases, Ninth Revision; SMRs: standardized mortality ratios.

Concomitant substance abuse

Studies in patients with schizophrenia have revealed that the prevalence of comorbid substance abuse varies from 15% to 65% [41 42]. In addition to nicotine, alcohol, cocaine and cannabis are frequently abused in patients with schizophrenia to the point that the comorbidity schizophrenia/cannabis has been characterised as epidemic [43]. Studies in emergency departments have shown that cannabis is the substance most frequently associated with acute episodes of schizophrenia and acute psychotic episodes, which also contributes to poor treatment outcomes in psychotic patients [44]. Moreover, several studies have highlighted that cannabinoids can produce a series of positive, negative and transitive cognitive symptoms in some healthy subjects [45]. The mechanism by which cannabinoids give rise to transitory psychotic symptoms in healthy and psychotic individuals remain unclear, but may involve neurotransmitters such as dopamine, GABA and glutamate.

The concept of schizophrenia

The current concept of schizophrenia originates from the description by Kraepelin of "dementia praecox" at the end of the 19th century (Lehrbuch der Psychiatrie, 1893) and from its re-elaboration at the beginning of the 20th century [46-48]. Considering psychotic disorders, Kraepelin distinguished two patterns of the course of disease and used these to define and classify two nosological entities: *dementia praecox*, which included catatonia, hebephrenia and paranoid states, and manic-depressive insanity, which comprised "folie circulaire" and melancholy. *Dementia praecox* was distinguished from manic-depressive insanity on the basis of its onset during adolescence or in early adulthood, chronic course and poor prognosis of the former, in contrast to the episodic nature and better prognosis of the latter.

During the same period, Bleuler (*Dementia Praecox, oder Gruppe der Schizophrenien*, 1911) proposed the term "schizophrenia" in place of *dementia praecox* to highlight that the distinctive characteristic of the disease is deficit in integration of different psychic functions (personality, thought, memory and perception). He believed that delirium and hallucinations were accessory symptoms that were variable and non-specific, and held that the fundamental symptoms were autism, ambivalence, affective flattening and the loosening of associative links of thought. Some of the symptoms described by Bleuler as fundamental, such as affective flattening, could also be denominated as "negative", since they represented a marked and attenuated pathology of normal psychic functioning. According to Bleuler, schizophrenia could have different grades of severity, and that it had latent and simple forms: in the latent form, which Bleuler thought was more common, all the different symptoms were present in some combination, while in the simple form the fundamental symptoms were present and the accessory symptoms were absent. He used the terms "schizophrenic group" to stress that it was a heterogeneous condition from a psychopathological standpoint and that its course, different from what Kraepelin proposed, was not seen as invariably chronic, but was characterised by a progressive deterioration of mental function.

Later, Schneider (*Clinical Psychopathology*, 1959) held that the fundamental defect of schizophrenia consisted in alteration of empathic communication. He identified some symptoms that are characteristic of schizophrenia and called them "the first range" to underline that the priority that he felt they should be part of the diagnostic procedure. These symptoms were incorporated in the definition of schizophrenia in the ICD-9 and DSM-III.

Diagnosis of schizophrenia using the main diagnostic systems

The diagnostic criteria of the DSM (from the first to fourth editions) and the ICD (from the 6th to 10th edition) for schizophrenia represented an attempt to integrate the various approaches described above, without having reached full harmonisation. The definitions of schizophrenia in the DSM-I to DSM-IV and in the ICD-6 to ICD-10 incorporated the chronicity of Kraepelin, the negative symptoms of Bleuler and the positive symptoms (of the first range) of Schneider as part of their definition. The emphasis placed on these three aspects, however, has changed over time. During the 1960s and 1970s there was no significant discrepancy between the DSM (I and II) and ICD (7 and 8) on this aspect. While the DSM-I and the DSM-II highlighted the Bleulerian prospective (emphasis on negative symptoms and broad definition of schizophrenia, including the latent, pseudoneurotic, pseudopsychopathic and residual forms), the ICD-7 and ICD-8 both highlighted the Kraepelinian chronicity. The excessively broad definition of schizophrenia in the DSM system is responsible for the low reliability of a diagnosis of schizophrenia and the marked discrepancies present in the USA and countries that use the ICD. In reaction to these anomalies, the working criteria of the DSM-III limited the definition of schizophrenia, with particular attention to the Kraepelinian chronicity and to the positive symptoms of Schneider (of the first range). In reality, the aim of greater reliability and conviction that the positive symptoms can be diagnosed with greater dependability have led to the fact that the positive symptoms have been considered as a fundamental characteristic of schizophrenia in the DSM-III and the ICD-9.

Both the DSM-IV and ICD-10 include the fundamental symptoms of Bleuler in diagnostic criteria and assign positive symptoms in the first range of Schneider with distinct priority, to the extent that only one of these symptoms is needed for diagnosis, while among the other symptoms only two are needed. The DSM-IV modified with Kraepelin criteria place emphasis on the chronicity of the disorder in that a duration of disease of at least 6 months is needed for diagnosis (at least 1 month during which the required symptoms are present for diagnosis and at least 6 months overall, considering prodromic and residual symptoms). It is currently believed that these criteria may preselect patients with unfavourable prognosis [49]. The ICD-10 limits the duration of symptoms to one month, in agreement with the idea of Bleuler in which schizophrenia does not necessarily present a chronic course; to avoid the consequent need to create an additional diagnostic category corresponding to schizophreniform, in the DSM-IV diagnosis was based only on duration of symptoms. The influence of

the Kraepelinian vision on the DSM-IV is also inferable to the presence of "functional criteria", or the need to identify social and employment dysfunction for diagnosis; such criteria are not present in the ICD-10. The Bleulerian vision of schizophrenia as a heterogeneous condition foresees the presence of subtypes at diagnosis on the basis of dominant symptoms: paranoid if delirium and hallucinations are dominant, disorganised (hebephrenic) if speech/disorganised behaviour prevail and/or negative symptoms, catatonic if movement disorders are most prominent, undifferentiated if there is no clear predominance of a cluster symptomatology and residual if only negative symptoms or productive symptoms are present in an accentuated form. The classification of subtypes in the ICD-10 is basically superimposable with that of the DSM-IV, except the presence of schizophrenia simplex, post-schizophrenic depression and not otherwise specified schizophrenia (Table VII).

Modifications to the diagnostic criteria of schizophrenia in the DSM-5 and in the available draft of the ICD-11 [51 52] have been modest overall and have not overcome the main differences, or those relative to temporal and functional criteria (Table VIII). In fact, the minimum duration of disease is still 6 months in the DSM-5 and 1 month in the ICD-11. Compromises in social and work functioning are needed for diagnosis in the DSM-5, but not in the ICD-11. However, in both systems, important modifications were made in the definition of the characteristic symptoms needed for diagnosis: the priority given to first range symptoms has been eliminated, for which at least two symptoms are needed to satisfy criterion A of schizophrenia, and at least one psychotic symptom is needed (delirium, hallucinations or disorganised thought). Moreover, the diagnostic subtypes have been eliminated since their reliability has been revealed to be rather limited and have limited diagnostic dependability and utility considering a research context and implementation of treatment programmes. In the attempt to favour a dimensional approach to diagnosis, in both the DSM-5 and the draft of the ICD-11, the use of psychopathological dimensions has been introduced that may lead to substantial improvement in describing individual clinical cases, and allow for better documentation of the heterogeneity of the disorder and at the same time to favour targeted and personalised treatment. In past years, the presence of diverse psychopathological domains has been well documented that present clinical courses, patterns of response to treatment and prognoses, and that present either alone or in combination in individual patients (Table IX).

The severity of each psychopathologic dimension varies among patients and even in same patient at different stages of the disease; measuring severity during the course of the disease and in the context of treatment can provide information that is useful for the clinician in evaluating the impact of treatment on the different dimensions. For example, it has been demonstrated that the prevalence of positive symptoms is associated with good response to treatment with antipsychotics [55 56], while severe cognitive alterations can predict poor response to treatment and poor prognosis [56]. A dimensional approach should encourage the physician to explicitly assess and monitor modifications in severity of each dimension and to use this information to guide treatment. A broad application of the dimensional approach should also contribute to research efforts on the aetiopathogenesis of the disease and in improving the presently used diagnostic categories. In the DSM-5, a total of 8 dimensions are described (hallucinations, delirium, disorganised thought, disorganised behaviour/alteration in motor behaviour, negative symp-

TABLE VII.
ICD-10 criteria for diagnosis of schizophrenia (from Meyer and MacCabe, 2012, modified) [50]. *Criteri ICD-10 per la diagnosi di schizofrenia (da Meyer e MacCabe, 2012, mod.)* [50].

ICD-10 for schizophrenia (F20)[a,b]	
At least one of the following:	
•	Thought echo, thought insertion or withdrawal, or thought broadcast
•	Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perception
•	Hallucinatory voices giving a running commentary on patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body
•	Persistent delusions of other kinds that are culturally inappropriate and implausible (e.g. being persecuted by a network of government agents; being as emissary from another world)
Or at least two of the following:	
•	Persistent hallucinations in any modality, when occurring every day for at least a month, when accompanied by fleeting or half-formed delusions without clear affective component, or when accompanied by persistent overvalued ideas
•	Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech
•	Catatonic behaviour, such as excitement, posturing, or waxy flexibility, negativism, mutism and stupor
•	Negative symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses
Duration of the above symptoms for at least 1 month	

[a] ICD-10 classification of mental and behavioural disorders, diagnostic criteria for research; [b] DSM-IV criteria specify a minimum duration of illness of 6 months, and includes a criterion for social and occupational dysfunction.

TABLE VIII.
Diagnostic criteria for schizophrenia in DSM-5 compared with DSM-IV (from Tandon et al., 2013, modified) [53]. *Criteri diagnostici della schizofrenia nel DSM-5 rispetto al DSM-IV (da Tandon et al., 2013, mod.)* [53].

DSM-IV criteria for schizophrenia	Proposed criteria for schizophrenia in DSM-5
Criterion A. Characteristic symptoms	**Criterion A. Characteristic symptoms: (minor change)**
Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated) (1) Delusions (2) Hallucinations (3) Disorganized speech (4) Grossly disorganized or catatonic behaviour (5) Negative symptoms, i.e., affective flattening, alogia, or avolition	Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated) At least one of these should include 1-3 1. Delusions 2. Hallucinations 3. Disorganized speech 4. Grossly disorganized or catatonic behaviour 5. Negative symptoms (i.e., diminished emotional expression or avolition)
Note: only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other	Note: Deleted
Criterion B. Social/occupational dysfunction: for a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement)	Criterion B. Social/occupational dysfunction (No change)
Criterion C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences)	Criterion C. Duration of 6 months (No change)
Criterion D. Schizoaffective and major mood disorder exclusion Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods	Criterion D. Schizoaffective and mood disorder exclusion No change
Criterion E. Substance/general mood condition exclusion Substance/general medical condition exclusion: the disturbance is not attributed to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition	Criterion E. Substance/general mood condition exclusion No change
Criterion F. Relationship to global developmental delay or autism spectrum disorder If there is a history of autism spectrum disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated)	Criterion F. Relationship to global developmental delay or autism spectrum Disorder - Minor change If there is a history of autism spectrum disorder or other communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated)

toms, cognitive deficits, depressive symptoms and manic symptoms), and each has a score that ranges from 0 to 4. In the ICD-11, a total of 6 dimensions are described, called "symptom specifiers", that include positive, negative, depressive, manic and psychomotor symptoms, and cognitive deficits. The inclusion of cognitive function in both systems represents an important new aspect compared with the previous versions of the DSM and ICD. In fact, evaluation of cognitive function was not expected in the previous classification systems, with the result that even today in many clinical contexts the necessary experience and instruments for basic neuropsychological evaluation is still lacking. This is in spite of the empirical evidence relative to the presence of numerous cognitive deficits in patients with schizophrenia, the impact of such deficits on functioning of the patient in the community and on the efficacy of cognitive training in a rehabilitative setting [57-60].

Unfortunately, in the DSM-5 the dimensions have been placed in Section 3, which includes instruments for evaluation and measurement, and will thus likely not be used to a large extent by clinicians. In contrast to the DSM, in the draft of the ICD-11 the dimensions are presently included in the chapter on "Schizophrenia and other primary psychotic disorders", which would indicate broader use among clinicians.

Specifiers of the course of disease

There is significant variability in the course of disease in patients with schizophrenia, and a wide range of factors must be considered to understand this aspect. In this regard, it is necessary to define both the present state (transversal specifier) and the longitudinal pattern of the disease (longitudinal specifier) in each patient (Table X).

The indicators of the transversal course can help understand if the patient responds fully or in part to the criteria of the active phase of schizophrenia, and if the present state is an episode or a partial or complete remission, or a continuous state of the disease. Moreover, it can be understood if the patient with an episodic course is experiencing the first or one of many episodes. Even if the transversal indicators are defined, these specifiers require a minimal observation period to be characterised. In contrast, specifiers of the longitudinal course of disease, which require an observation period of at least one year, describe the longitudinal behaviour of the disease in a single patient, and is characterised as episodic or continuous.

Attenuated psychotic syndrome

It is believed that the unsatisfactory prognosis of schizophrenia in a significant proportion of patients is due to the late identification and start of treatment, and thus the individual has already suffered significant psychopathologic damage. The introduction of attenuated psychotic syndrome in the DSM-5 is aimed at helping clinicians recognise and monitor the presence of psychotic symptoms in the initial phase, and if needed, to intervene during this crucial stage. However, even if the recognition of attenuated psychotic syndrome is important, the ability to actually diagnose this condition in routine practice has not been demonstrated and its relation with other nosological entities has not been precisely defined; for this reason, this syndrome is not contained within the main body of the DSM-5, but rather in Section 3 as a condition for which further study is needed. It should be stressed that diagnosis of attenuated psychotic syndrome does not represent an indication, in itself, for antipsychotic treatment, although it should prompt careful examination for comorbidities (anxiety, depression, substance abuse disorders, etc.) and appropriate treatment, together with accurate follow-up for a possible transition to psychosis.

Differential diagnosis with schizoaffective disorder

The term "schizoaffettive disorder" (*Schizo-Affective Disorder*, SAD) was coined in the 1930s to define patients who presented with characteristics of both schizophrenia and affective disorder [61]. Until the DSM-IV, schizoaffective disorder was divided into two types, depressive and bipolar; in the DSM-IV-TR it was affirmed that schizoaffective disorder filled a necessary and important place in the diagnostic system, but unfortunately did not fulfil its role (DSM-IV-TR Sourcebook). In particular, the fact that specific criteria for duration of mood alteration were lacking was a problem, and could constitute the main cause for the low reliability of diagnosis of schizoaffective disorder. Another limitation is the fact that the temporal stability in the DSM-IV diagnosis of schizoaffective disorder in not entirely clear, and appears to be notably less than schizophrenia, bipolar disorder and major depression.

In schizoaffective disorder, the aim of the DSM-5 was to increase reliability and to introduce symptom dimensions that provide data for future conceptualisations of chronic psychotic conditions [61-63]. Thus, in the DSM-5 criterion C for schizoaffective disorder is defined with very stringent criteria. In fact, to meet criteria for schizoaffective disorder it is required that the symptoms affecting mood are sufficient to satisfy the criteria for an episode of a major mood disorder for at least half the total duration of the disease since the beginning of the first psychotic episode, including the prodromal and residual phases (Table XI). In this sense, in the DSM-5 schizoaffective disorder is a stable diagnosis that considers the time from the onset of psychosis up to the present episode rather than defining a single episode with comorbid psychotic and mood symptoms.

TABLE IX.
Dimensional assessment of symptoms and related clinical phenomena for psychosis in DSM-5 (from Barch et al., 2013, modified) [54]. *Valutazione dimensionale dei sintomi nella psicosi nel DSM-5 (da Barch et al., 2013, mod.)* [54].

Hallucinations	Delusions	Disorganized speech	Abnormal psychomotor behaviour	Negative symptoms (restricted emotional expression or avolition)	Impaired cognition	Depression	Mania
0. Not present	Not present	Not present	Not present	Not present	Not present	Not present	Not present
1. Equivocal (severity or duration not sufficient to be considered psychosis)	Equivocal (severity or duration not sufficient to be considered psychosis)	Equivocal (severity or duration not sufficient to be considered disorganization)	Equivocal (severity or duration not sufficient to be considered abnormal psychomotor behaviour)	Equivocal decrease in facial expressivity, prosody, gestures or self-initiated behaviour	Equivocal (cognitive function not clearly outside the range expected for age or SES, i.e., within 0.5 standard deviation (SD) of mean)	Equivocal (occasionally feels sad, down depressed or hopeless; concerned about having failed someone or at something but not preoccupied)	Equivocal (occasional elevated, expansive or irritable mood or some restlessness)
2. Present, but mild (little pressure to act upon voices, not very bothered by voices; delusions are not bizarre, or little pressure to act upon delusional beliefs, not very bothered by belief)	Present, but mild (delusions are not bizarre, or little pressure to act upon delusional beliefs, not very bothered by beliefs)	Present, but mild (some difficulty following speech)	Present, but mild (occasional abnormal or bizarre motor behaviour or catatonia)	Present, but mild decrease in facial expressivity, prosody, gestures or self-initiated behaviour	Present, but mild (some reduction in cognitive function below expected for age and SES, b/w 0.5 and 1 SD from mean)	Present, but mild (frequent periods of feeling very sad, down, moderately depressed or hopeless; concerned about having failed someone or at something with some preoccupation)	Present, but mild (frequent periods of somewhat elevated, expansive or irritable mood or restlessness)
3. Present and moderate (some pressure to respond to voices, or is somewhat bothered by voices)	Present and moderate (some pressure to act upon beliefs, or is somewhat bothered by beliefs)	Present and moderate (speech often difficult to follow)	Present and moderate (frequent abnormal or bizarre motor behaviour or catatonia)	Present and moderate decrease in facial expressivity, prosody, gestures or self-initiated behaviour	Present and moderate (clear reduction in cognitive function below expected for age and SES, b/w 1 and 2 SD from mean)	Present and moderate (frequent periods of deep depression or hopelessness; preoccupation with guilt, having done wrong)	Present and moderate (frequent periods of extensively elevated, expansive or irritable mood or restlessness)
4. Present and severe (severe pressure to respond to voices, or is very bothered by voices)	Present and severe (severe pressure to act upon beliefs, or is very bothered by beliefs)	Present and severe (speech almost impossible to follow)	Present and severe (abnormal or bizarre motor behaviour or catatonia almost constant)	Present and severe decrease in facial expressivity, prosody, gestures or self-initiated behaviour	Present and severe (severe reduction in cognitive function below expected for age and SES, > 2 SD from mean)	Present and severe (deeply depressed or hopeless daily; Delusional guilt or unreasonable self-reproach grossly out of proportion to circumstances)	Present and severe (daily and extensively elevated, expansive or irritable mood or restlessness)

TABLE X.
Common definitions for generic terms describing the course of disease in the DSM-5 (from Tandon et al., 2013, modified) [53].
Definizioni comuni dei termini relativi alle caratteristiche del decorso nel DSM-5 (da Tandon et al., 2013, mod.) [53].

Term	Definition
Episode	An episode is a specified duration of time in which the patient has developed symptoms that meet the symptomatic criteria of a given mental disorder. Note that these – depending on the type of mental disorder – may imply a certain number of symptoms, or a specified severity or frequency of symptoms. Episodes may be further differentiated into a single (first) episode or recurrence or relapse of multiple episodes if appropriate
First episode	First manifestation of a disorder meeting diagnostic symptom and time criteria (single episode: episode that occurs once in a lifetime, has not been preceded by another episode, and ends with full or partial remission. Can only be diagnosed retrospectively)
Multiple episodes	May be determined after minimum 2 episodes, i.e., after a first episode and minimum one remission/relapse, or after multiple episodes. May be further specified as with partial or full inter-episode remission
Remission	Remission occurs when disorder-specific symptoms have not been present for a period of time. May be further specified as partial or full
Partial remission	Partial remission is a specified time period during which an improvement of a defined magnitude after a previous episode is maintained and in which the defining criteria of a given mental disorder are only partially fulfilled
Full remission	Full remission is a specified period of time after a previous episode during which no disorder-specific symptoms are present. Continuous symptoms fulfilling the diagnostic symptom criteria of a disorder are remaining for the majority of the illness course with subthreshold symptom periods being very brief relative to the overall course

In the ICD-11, the attempt to improve diagnostic criteria for schizoaffective disorder are based on two concepts: 1) elimination of subtypes (manic, depressive and mixed) that are substituted with the "symptom specifiers" previously mentioned for schizophrenia, and 2) use of more stringent symptomatological criteria: in fact, instead of requiring, as in the ICD-10, that affective and schizophrenic symptoms must be prominent in the same episode, in the ICD-11 the symptomatic criteria for schizophrenia and major depression, manic, or mixed episodes must be present in the same episode.

The initial phases of schizophrenia

The course of psychosis can be divided into three phases: premorbid psychosis, prodromic and florid, even if the first two phases are often identifiable retrospectively only after the first genuine overt episode of psychosis [64]. The premorbid phase is a period of relative normality before the patient demonstrates any psychotic symptoms (although other symptoms such as anxiety or depression may be present). The prodromic phase is characterised by an accelerated decline in global functioning and the emergence of psychotic symptoms. The florid phase refers to the appearance of the typical symptoms of the disease. An initial prodromic phase can be demonstrated in about 75% of patients with the first psychotic episode; this initial phase lasts around 5 years, has a pathological significance and brings about psychosocial deficits [64-66]. Even if many symptoms in the prodromic phase are non-specific and it is difficult to distinguish from other psychiatric conditions such as depressive, some syndromes seem to allow early identification, and thus the possibility to initiate preventive treatments [64 65]. The symptoms and prodromic behaviours schizophrenia include alterations in mood (depression, anxiety, dysphoria and irritability), cognitive symptoms (distractibility and difficulty concentrating), social withdrawal, obsessive behaviours, and especially after the premorbid phase, even short lasting positive symptoms (delirium, ideas of reference, magical thinking).
According to data from the ABC Study [67], 73% of first episodes initiate with specific prodromal symptoms or with negative symptoms, 20% with positive or negative symptoms or non-specific symptoms and 7% with positive symptoms alone. In only 18% of cases does schizophrenia show an acute onset with symptoms that appear within one month, while 68% have insidious onset with the first symptoms that appear after more than a year before the first hospitalisation. The psychotic part of the first episode, which extends from the first episode, and extends from the first until the appearance of positive symptoms, lasts an average of about 1 year and the first admission occurs on average after 2 months.

It has been demonstrated that the duration of untreated psychosis (DUP) is negatively associated with long-term symptomatic and functional outcomes in patients with schizophrenia [64 65 68 69]. Moreover, some studies have indicated that cognitive function deteriorates rapidly before the full manifestation of psychotic symptoms. Therefore, it is believed that intervention during the initial phases of the disease may reduce the DUP and/or help to preserve the overall functional capacity of the individual by addressing the deterioration of functioning that occurs before the first psychotic episode. In fact, a prolonged DUP has been associated with delayed and incomplete remission of symptoms, the presence of persistent negative symptoms [70], longer duration of hospitalisation and greater risk of recurrence, increased risk of depression and suicide, greater substance abuse and delinquent behaviour and significantly higher treatment costs.

Models of care and assistance in Italy

Recently, the WHO has proposed a Plan of Action for 2013-2020 to favour the commitment of governments in increasing the priority given to mental health as part of public health policies [71]. The plan is ambitious: a world in which mental health is appreciated and promoted, mental disorders are prevented and affected individuals are able to access culturally appropriate, high-quality medical and social care, in a timely manner, exercise the full range of human rights to achieve the highest possible level of health and to participate fully in a society free from stigma and discrimination. In particular, regarding mental health services, the plan calls for five actions: reorganisation and expansion of coverage of services, integrated care and timely mental health in humanitarian emergencies, development of human resources and elimination of disparities.

It has been suggested that, as essential members of a team providing services, psychiatrists can facilitate the efficient use of the available resources, and in particular those available to less specialised healthcare operators, such as general practitioners, nurses and other healthcare operators [72].

In reality, more than 30 years after the approval of law 180/78, which decentralised treatment of psychiatric patients, and the beginnings of local psychiatric services in Italy, the network of local services for mental health care in Italy likely represents, on an international level, a model to be adopted in the development of community interventions.

The Department of Mental Health (Dipartimento di Salute Mentale; DSM), which constitutes the collection of structures and services that have the job of meeting mental health needs, as well as assistance and protection of mental health within the territory defined by community healthcare services, has facilities for day care (Centri di Salute Mentale, CSM), semi-residential services (Centri Diurni, CD), residential (residential structures, divided into therapeutic-rehabilitative and socio-rehabilitative residences) and hospital-based services (Psychiatric Departments with day hospital services) [73 74]. The CSM provides a large part of outpatient and non-residential assistance and coordinates all preventive, curative and rehabilitative interventions on a community level for subjects with psychiatric pathologies; the service is active for outpatient and home visits at least 12 hours a day, 6 days a week.

In accordance with its mandate, mental health services primarily provide care for severe mental disorders (psychosis, severe depression and bipolar disorders). Services can be accessed in two ways: by direct access, directly at a CSM, or by request of a general practitioner or Emergency Department after evaluation. Patients that contact the CSM must be evaluated within a relatively short period (7 days if case of emergency or within 21 days if the access has been programmed) by specialist and multidimensional (psychosocial) examination. For patients with severe psychiatric disorders in which short-medium term treatment is anticipated, in addition to outpatient/home visits, if needed, treatment can be carried out at residential or semi-residential structures with the aim of establishing an intensive therapeutic programme and socio-rehabilitative course. Hospitalisation should be limited to acute, severe episodes and remission of symptoms; maintenance therapy is performed by community healthcare services. Following discharge from a psychiatric department, the patient's course must be monitored by community services and rehabilitative therapies and treatment must be established.

In the last decade, at national and regional levels, the efficiency of the community psychiatric system has been assessed system in terms of level of care provided to patients with psychoses, and in particular, with schizophrenia.

In 2008, the Italian National Institutes of Health launched the SEME (Sorveglianza Epidemiologica in salute Mentale) programme, which had the objective of realisation of epidemiological monitoring based on a network of 22 satellite CSM in order to: 1) accurately and reproducibly identify new cases of severe mental disturbances; 2) measure the frequency of new diagnoses and describe their evolution over time; 3) describe the characteristics of the patient's journey, management by psychiatric services and assess the impact on the patient's health. Considering psychotic disorders (schizophrenia, schizophreniform disorders, schizoaffettive disorders, delirium), data from the study [19] showed that the raw incidence was 17.7 cases per 10,000 person-years (with large geographic differences) with a median time between appearance of symptoms and presentation to mental health services of 5 years, which was similar to bipolar disorder and an-

orexia, and greater than major depression (2 years). This is reflective of a marked delay in treatment of psychiatric disturbances due to the lack of early access to services by patients, in agreement with international data [75]. The reasons for this delay are related to the lack of insight about the disease by patients, reluctance to ask for help and social stigma [19].

Any judgement regarding the efficacy of mental health services cannot be complete without evaluating the outcomes of interventions, which represents a central but difficult task. In fact, significant positive outcomes, or improvement in health following intervention, are the primary goal of mental health services. However, while challenging, the choice of methods and instruments to measure outcomes requires an equilibrium of conceptual, ethical and clinical considerations. In a recent publication by Throniscroft and Slade, [76] a taxonomy of clinical decisions was proposed that investigators must consider when evaluating outcomes of mental health interventions. Such a proposal should be taken into consideration to improve the ability to evaluate the efficiency of services offered. The problem of determining the right indicators to evaluate the treatment journey of patients with mental disorders was examined by the Management Laboratory at the Sanità della Scuola Superiore Sant'Anna di Pisa, whose recommendations were then submitted to a parliamentary commission on the efficacy and efficiency of national health services in Italy [77].

In practice, the PROG-CSM (Progetto Centri di Salute Mentale) [78] study examined all CSM with the aim of evaluating the level of adherence of centres to the standards of a large project for protection of mental health. Indicators were used to measure the continuity of care, coordination with other community services outside the CSM, patient accessibility and implementation of specific programmes destined for certain types of patients or needs for care. The PROG-CSM revealed that there was a high overall level of adherence by the CSMs concerning continuity of care and coordination with other local services, although the levels of accessibility and implementation of specific programmes was lower.

The discrepancies between the available evidence and routine clinical practice were studied in a project sponsored by the Società Italiana di Epidemiologia Psichiatrica (DIRECT'S Project: *DIscrepancy between Routine practice and Evidence in psychiatric Community Treatments on Schizophrenia*) in 19 CSM [79]. The study revealed that discrepancies were more frequently represented by: lack of written materials, guidelines and providing systematic information to clients; lack of monitoring and assessment of interventions; difficulty in implementation of specific forms and structures for intervention; difficulty in considering family members of patients as having a role that requires that their participation in the treatment process; a background oriented in a psychodynamic sense considering healthcare personnel; a complete lack of knowledge regarding discrepancies between guidelines and routine practice in some treatment situations that could represent a genuine problem, and that overcoming this requires specific formation and initiatives.

In a publication in the *Annali dell'Istituto Superiore di Sanità* [74], the Italian psychiatric system was reviewed, and even if there is still some variability in the level of care among different regions, in general it was considered to be well structured and efficient. The CSMs appear to be highly accessible and treat the majority of patients with severe and non-severe psychiatric disorders. In contrast, the availability of hospital-based assistance shows significant differences between geographic regions in terms of the number of beds and type of patients admitted. In the same publication, as an indicator of the quality of Italian psychiatric services was indicated, the treatment gap, or the percentage of subjects that present with disease but who are not cured, was considered. According to reasonable calculations, at least considering the data from 3 northern regions (Friuli-Venezia Giulia, Lombardia and Emilia Romagna), the data for schizophrenia was similar, around 57% [74], comparable to that seen in other European countries (e.g. the NEMESIS study in The Netherlands).

The quality of local psychiatric assistance in Italy was also evaluated by several studies on a regional level. In a retrospective analysis by Lora et al. [23], the adequacy of psychiatric treatment provided by the Lombardia region to patients with schizophrenia spectrum disorders and mood disorders was analysed. In that study, carried out on more than 44,000 patients, it was determined that about 50% of those with severe mental disorders did not receive adequate assistance; in particular, 45.5% of those with depressive disorders, 55.7% of those with bipolar disorder and 49.3% of patients with schizophrenia spectrum disorders were considered to receive minimally adequate treatment that was in line with the recommendations of the American Psychiatric Association. The authors concluded that the improvements that need to be implemented include continuity of outpatient care, which requires the allocation of more resources to the CSM, and adherence to treatment, which requires a better partnership between the doctor and patient.

Regarding continuity of care, another study [80] evaluated the changes in continuity of care and the type of "care packet' used from 1999 to 2009. The study demonstrated that in Lombardia, for schizophrenia in adult patients (> 17 years), the number of subjects with continuity of care was relatively unchanged considering 15.5/10,000 (55%) in 1999 and 21.2/10,000 (57%) in 2009. Regarding the type of care packet used, it should be noted that the percentage of patients followed by *Community packages* (in

TABLE XI.
DSM-5 criteria for schizoaffective disorder (from Malaspina et al., 2013) [61]. *Criteri DSM-5 per il disturbo schizoaffettivo (da Malaspina et al.,2013)* [61].

A.	An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with Criterion A of schizophrenia. Note: the major depressive episode must include Criterion A1
B.	Depressed mood. Delusions or hallucinations for 2 or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness
C.	Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of the illness
D.	The disturbance is not attributable to the effects of a substance or another medical condition

Specify whether:
Bipolar type: this subtype applies if a manic episode is part of the presentation.
Major depressive episodes may also occur.
Depressive type: this subtype applies if only Major depressive episodes are part of the presentation.
With catatonia: this specifier, which applies to both 295.70 (F25.1) schizoaffective disorder, with prominent depressive symptoms, and 295.70 (F25.0). Schizoaffective disorder, with prominent manic symptoms, may be used to specify a current episode with at least three of the following: catalepsy, waxy flexibility, stupor, agitation, mutism, negativism, posturing, mannerisms, stereotypies, grimacing, echolalia and echopraxia.

addition to clinical care by healthcare professionals, also received social assistance and rehabilitation therapy) decreased from 47% in 1999 to 43% in 2009, with a corresponding increase in *Clinical packages* (in which patients are followed only by clinical healthcare professionals such as psychiatrists and psychologists) from 23% to 27%. This latter observation, in addition to the increased social inclusion of new patients that use local services, is probably related to the increasing difficulty of CSMs to provide expensive integrated care. The complexity of a multi-disciplinary team does not seem to be fully appreciated, and the opportunities that such a team provide do not seem to be exploited completely, especially in the evaluation and assessment phases.

An important attempt at improving and integrating the services offered at the community level in diagnosis and treatment of some psychiatric disorders is being achieved through several innovative programmes. In particular, one of the local programmes is dedicated to diagnosis and early intervention in individuals with a first episode of schizophrenia. In a recent report [81] on the so-called Programma2000 study, the first Italian programme on identification and early intervention following onset of mental disorders, involving 206 subjects with an age between 17 and 30 years (110 with a first episode of schizophrenia, 96 ay high risk of progression to psychosis), the mean duration of untreated illness (DUI) was, respectively, 30.1 and 30.7 months, while the mean duration of untreated psychosis (DUP) was 160.5 days for the first episode of schizophrenia. Several international studies have shown that early intervention programmes can favour a reduction in both DUI and DUP [82]. Importantly, early intervention can delay the onset of psychotic symptoms, reduce disease severity and counteract the biological, psychological and social consequences. Moreover, since it also plays a crucial role in decreasing deterioration of social functioning in the phases during which the psychosis has not yet manifested, it is hoped that similar early intervention programmes can be initiated at all Italian CSMs.

In conclusion, community psychiatric services can work together with the goal of overcoming the need for asylums: if the job of asylums was to preserve society from deviance, for community psychiatric services the main task is to promote mental health in individuals with psychiatric disorders. The level of care of community psychiatric services can be considered good, but there is still work to do. In particular, there is the need for computerised national and regional databases, which are still not available in some regions in Italy [74]; systems for monitoring and registering pathologies and treatments utilised is essential to improve the efficiency of services and integration with other psychiatric care structures (residential, hospital). The possibility to implement innovative programmes that are integrated with the routine activities of local services can help improve the quality and timeliness of care, for example, by reducing the duration of untreated illness, the consequences of the disease and deterioration of social functioning of affected individuals. Two fundamental principles for any activity in this activity are worthy of mention. The first is that the psychiatrist must always be available for communication with the patient. Only continuous availability can allow the clinician to see that each disorder is not static, but rather a complex of phenomena, which reveal the problematic areas of the relationship between the individual and the environment, and between the individual and his/her disorder. In this sense, the unremitting application of a "local principle" requires the effort to reopen and keep open

routes that tend to close [83]. The other fundamental point is the need for a therapeutic alliance between patients and community psychiatric services, and in particular between the client, family members and healthcare providers [84]. As in all developed countries, greater valorisation of the needs of the client should be the cornerstone of such services. This is a concrete aspect of healthcare services that are client orientated, which should be a model to follow in any field of medicine.

Conflict of Interest

Carlo Altamura has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Roche, Lundbeck, Merck, AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Sanofi, Eli Lilly, Pfizer and Otsuka.
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Silvana Galderisi has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Janssen-Cilag, Roche, Otsuka, Lundbeck, Pierre Fabre e Amgen-Dompé.
Paola Rocca has participated as speaker on symposia for Bristol-Myers Squibb, Janssen-Cilag, Otsuka, Roche.
Alessandro Rossi has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Takeda, Roche, Lundbeck, Janssen-Cilag.

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