



First episode psychoses in people over-35 years old: uncovering potential actionable targets for early intervention services

Maria Ferrara^{a,b,c,*}, Ilaria Domenicano^a, Aurora Marchi^a, Giulia Zaffarami^a, Alice Onofrio^a, Lorenzo Benini^c, Cristina Sorio^c, Elisabetta Gentili^d, Martino Belvederi Murri^{a,c}, Tommaso Toffanin^{a,c}, Julian Little^{a,e}, Luigi Grassi^{a,c}

^a Institute of Psychiatry, Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy

^b Department of Psychiatry, Yale School of Medicine, New Haven CT, USA

^c Department of Mental Health and Pathological Addiction, Local Health Trust (AUSL) Ferrara, Ferrara, Italy

^d Department of Engineering, University of Ferrara, Ferrara, Italy

^e School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada

ARTICLE INFO

Keywords:

Women

Early psychosis

Sex differences

Psychosis vulnerability

Early intervention

ABSTRACT

The traditional youth-oriented design of Early Intervention Services (EIS) may lead to the exclusion of patients who have their psychotic onset later in life. A retrospective study was conducted to compare first-episode psychosis (FEP) patients who accessed treatment when aged ≤ 35 years with those $\geq 36+$. A total of 854 patients were identified among 46,222 individuals who had access to community psychiatric services from 1991 to 2021. FEP were aged 18–65, received care between 2012 and 2021 and had a diagnosis of affective or non-affective FEP. Two groups were identified (FEP diagnosed at age ≤ 35 vs ≥ 36) and compared for sociodemographic and clinical characteristics. Most patients were diagnosed when aged $\geq 36+$ (61.8%). Compared to the ≤ 35 group, older patients were more likely to be women, married and diagnosed with affective psychosis, and they were less frequently hospitalized. Long-acting injectables antipsychotics (LAI) were less frequently prescribed in the $\geq 36+$ group, whereas antidepressants were more frequently prescribed compared to those aged ≤ 35 . In both age groups, women were less frequently prescribed LAIs compared to men. These findings highlight the need to reorient EIS to accommodate the needs of older FEP, especially women.

1. Introduction

The definition of first episode psychosis (FEP) is usually operationalized as the first appearance of positive psychotic symptoms, including hallucinations, delusions, and disorganized behavior (Breitborde et al., 2009a). The evolution of the condition largely depends on the timing and quality of initial therapeutic management (de Girolamo et al. 2012): the duration of untreated psychosis (DUP, i.e. the time between the onset of psychosis and receipt of adequate treatment (Breitborde, Srihari, and Woods 2009b)) and longer DUP is associated with worse outcomes and prognosis (Srihari et al. 2022; Penttila et al. 2014). Delayed or suboptimal treatment increases the risk of the condition becoming chronic, with more serious symptoms, worse response to pharmacological treatment, educational and employment failure, self-injurious behavior and suicide (Large and Nielsen 2011), worse interaction with the criminal justice system (Pollard et al. 2020), poor

interpersonal relationships, and worse quality of life (Challis et al. 2013; Marshall et al. 2014).

For these reasons, early intervention programs (EIP) for FEP have been implemented worldwide (Correll et al. 2018), with the goal of identifying patients with psychotic symptoms early in the course of illness. FEP programs traditionally target adolescents and young adults as the mean age of psychosis onset is reported across studies to lie between the age of 15 and 35 years (median 22–23). The male proportion is 75%. EIP adopt youngster-friendly language and offer youth-oriented treatment (McGorry 2007) (Pollard, Cahill, and Srihari 2016) including vocational support in order to help patients return to school or find an occupation, provide social-skills training, individual psychological treatment, family interventions to reduce the family burden and improve the caregiving experience, and specialized integrated services to reduce substance abuse (Fusar-Poli, McGorry, and Kane 2017; McGorry, Killackey, and Yung 2007).

* Corresponding author.

E-mail address: maria.ferrara@unife.it (M. Ferrara).

<https://doi.org/10.1016/j.psychres.2024.116034>

Received 15 February 2024; Received in revised form 25 March 2024; Accepted 13 June 2024

Available online 16 June 2024

0165-1781/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

However, recent evidence has shown that a substantial portion of individuals have their onset later in life (Solmi et al. 2022), especially women, who show a secondary peak in incidence in their mid-late 40 s (Ferrara et al., 2023a; Jongasma et al. 2018; Kirkbride et al. 2012). Indeed in 2016 the National Institute for Health and Care Excellence (NICE) revised its guidelines about EIP (National Institute for Health Care Excellence 2016) expanding their age range to include patients up to the age of 65. The first studies that were conducted after the release of the new guidelines showed some interesting results. Jagger and collaborators explored the immediate implications of the guidelines' change and analyzed data from The Cambridgeshire and Peterborough EIP service (CAMEO). As expected, they reported a caseload increase: within 141 patients that met the EIP CAMEO inclusion criteria from April 2016 to June 2017, 51% were over-35s. Most of those over-35s were White-British, and most were women. Referrals for over-35s were more frequently received from acute and secondary mental health services, compared to under-35s that had their referrals more often from primary care. They also reported that older patients required more support from EIP health care professionals, more contacts with social workers, care-coordinators, psychiatrists, psychologists and general practitioners for physical illness (Jagger et al., 2020). DUP was longer in over-35s (up to 20 years) (Clay et al. 2018). Thakrar et al. in 2023 reported that The Psychosis Intervention and Early Recovery (PIER) team caseload in Leicester from 2017 to 2020 increased by 35%: while the proportion of males and under-35s decreased, they confirmed there was an increase of the proportion of females and patients over 35 years old (women represented the 62% of the over 35 cohort) (Thakrar, Bardhan, and Chakraborty 2023).

There are reports of initiatives from some EIP outside the UK such as the St. Vincent Hospital Melbourne (Australia), an adult public sector mental health service which accepts all patients aged 16–65 years presenting with FEP (Selvendra et al. 2014a). However, to our knowledge, the UK and Ireland are currently the only countries that offer FEP intervention systematically up to ages over 60 (65 in the UK, 64 in Ireland (Power 2019)).

In Italy, FEP patients aged 35 and above are currently excluded from mainstream FEP services and offered treatment as usual (Meneghelli et al. 2023). Moreover, as the main focus of research so far has been targeting younger FEP, there is no information available about the demographic and clinical characteristics of those with FEP older than 35 years in Italy. Thus, it is not possible to draw any conclusion on how hypothetical FEP services might look like in order to meet the needs of a likely different population of patients if FEP programs were to be offered to individuals above age 35. The challenges that older patients must face during their pathways to care and through care are very likely different from younger patients with FEP.

Therefore, to address this gap, we decided to conduct a study with this primary aim of comparing the sociodemographic and clinical differences between a group of patients who had access to psychiatric care for FEP while ≤ 35 vs those who were aged of 36 or more. The overall goal is to identify the specificities of each group and to hypothesize a new approach for those who have their FEP later in life.

2. Methods

2.1. The FEP Program in Ferrara, Emilia-Romagna region

In 2012, the Emilia-Romagna Health Care Agency prompted the implementation of a coordinated specialty care program for FEP and clinical high risk for psychosis within the age range of 15–35 (Belvederi Murri et al. 2021; Gruppo di lavoro Esordi Psicotici 2016), following the Italian Guidelines for Schizophrenia (De Masi et al. 2008). The Integrated Department of Mental Health and Substance Abuse in Ferrara immediately implemented an EIP program following the regional recommendations, later formalized as a Care Pathway (Belvederi Murri et al. 2021). The FEP Program provides a dedicated team that includes

psychiatrists, psychologists, specialists in Psychiatric Rehabilitation, nurses, educators, and social workers. The team offers a coordinated specialty care that differs from standard care in having a greater intensity of the interventions, a specific orientation towards personal and functional recovery, a normalizing approach towards the experience of psychosis, and a shared vision of hope and fight against chronicity (Gruppo di lavoro Esordi Psicotici 2016) (Fusar-Poli, McGorry, and Kane 2017; McGorry, Killackey, and Yung 2007). The initial reports of such program demonstrated the feasibility of its implementation, the effectiveness in reducing symptom burden, and promoting recovery (Belvederi Murri et al., 2023).

2.2. Population and study design

In Italy, psychiatric care is provided by 139 Departments of Mental Health (DMHs). The Integrated Department of Mental Health and Pathological Addictions (IDMHPA) of Ferrara includes three Community Mental Health Centres (CMHCs), two acute inpatient units, a Consultation-Liaison Psychiatry Service, a psychology service and three rehabilitation centres. The IDMHPA in Ferrara province covers an area of 2630 km², with a catchment of 342.061 inhabitants as of 2020 (Belvederi Murri et al. 2021).

In this retrospective study data were extracted from FEPSY, an anonymized database that includes information on 46,222 individuals that accessed to community mental health facilities of the Ferrara province between the years 1991 and 2021 (Ferrara et al., 2023a).

The patients included in the study were those who, between 2012 (the year when the regional recommendation for FEP were implemented in Ferrara (Belvederi Murri et al. 2021; Belvederi Murri et al. 2023; Ferrara et al. 2019) and February 2021, were aged between 18 and 65 years at their first access to CMHCs for FEP, and had a psychosis diagnosis eligible for the FEP Program in Ferrara, according to the local care pathway (thus affective and non-affective psychosis ever treated before for FEP) (ICD-9 295.*; 296.54; 296.14; 296.64; 296.44; 296.24; 296.34; 297.*; 298.*; 298.9; 299.90; 299.91) (Belvederi Murri et al. 2021). Individuals were excluded if they had severe intellectual disability (IQ < 50) or organic psychoses.

2.3. Variables

Demographic information including age at first visit, sex, country of birth (Italy vs other country), marital status, education level, and living condition were selected from FEPSY.

Clinical characteristics were also analyzed, including psychosis diagnoses (first psychosis diagnosis i.e., the first diagnosis at admission to the FEP program, last primary recorded diagnosis, i.e., the more recent diagnosis recorded in the clinical chart), and service pathways (psychiatric hospitalizations -number and duration-, psychotropic medication prescription at admission-type and dosage).

2.4. Statistical analysis

The patients identified were divided in two groups based on their age (≤ 35 or 36+) recorded at the first access to the community mental health service. A comparison between demographic and clinical characteristics was conducted between the two groups by bivariate analysis. The distribution of the age at admission to care was represented by using a kernel density distribution to reduce the effect of noise in the data. The density estimate was performed with a Gaussian kernel: the peak of the curve indicates where values are most concentrated (Parzen 1962; Rosenblatt 1956). A further comparison, by sex, was conducted relating to diagnoses and service pathways in each age group. Chi-squared tests and t-tests were performed to compare categorical variables and normally distributed variables, respectively. Mann-Whitney tests were used to analyze skewed continuous variables. P values less than 0.05 were considered to be statistically significant. All analysis were conducted

with the statistical software R.

2.5. Ethical approval

Ethical approval was obtained by the Area Vasta Emilia Centro Ethical Committee on December 12, 2019 (protocol number: 197/2018/Oss/AUSLF). This study conforms to the principles expressed in the Declaration of Helsinki.

3. Results

3.1. Socio-Demographic and clinical characteristics

Among the 854 individuals meeting the study’s criteria, the majority were 36+ (N = 528, 61.8%), as detailed in Table 1. As shown in Fig. 1, compared to the under-35s group, the older group had a substantially higher proportion of women (55.7% vs 32.5%, $p < 0.01$), while the under-35s were predominantly men (67.5%), and had double the proportion born abroad (35.9% vs 16.3%, $p < 0.01$). There were more single people in the under-35s (62.0% vs 30.3%, $p < 0.01$) and, on the contrary, more people married or divorced in older group.

Table 1
Demographic details of the clinical sample (N = 854).

	≤ 35 N = 326 (38.2%)	36+ N = 528 (61.8%)	p-value
Age at first visit, yrs			<0.01 ^a
Mean (SD)	27.0 (5.2)	49.1 (8.2)	
Median (min; max)	27 (18;35)	49 (36; 65)	
Sex assigned at birth, N (%)			<0.01 ^b
Male	220 (67.5)	234 (44.3)	
Female	106 (32.5)	294 (55.7)	
Place of birth, N (%)			<0.01 ^b
Italy	209 (64.1)	441 (83.5)	
Country other than Italy	117 (35.9)	86 (16.3)	
Missing	0 (0.0)	1 (0.2)	
Marital Status, N (%)			<0.01 ^b
Single	202 (62.0)	160 (30.3)	
Married / with Partner	20 (6.1)	146 (27.8)	
Separated/Divorced/Widowed	5 (1.5)	58 (11.0)	
Missing	99 (30.4)	163 (30.9)	
Education level, N (%)			<0.01 ^b
Illiterate	0 (0.0)	4 (0.8)	
Literate	6 (1.9)	20 (3.8)	
Primary school	19 (5.8)	32 (6.0)	
Middle school	58 (17.8)	136 (25.8)	
High school	101 (31.0)	115 (21.8)	
University	34 (10.4)	37 (7.0)	
Missing	108 (33.1)	184 (34.8)	
Living condition, N (%)			<0.01 ^b
Community housing facilities	15 (4.6)	5 (0.9)	
Alone	19 (5.8)	57 (10.8)	
With parents	112 (34.3)	85 (16.1)	
Own family	34 (10.4)	152 (28.8)	
Prison	0 (0.0)	3 (0.6)	
Retirement home	0 (0.0)	1 (0.2)	
Safe house	4 (1.2)	9 (1.7)	
With other family members	30 (9.2)	30 (5.7)	
With others	16 (4.9)	14 (2.7)	
Other	15 (4.6)	16 (3.0)	
Missing	81 (24.8)	156 (29.5)	
Catchment Area, N (%)			0.83 ^b
Cento	34 (10.4)	54 (10.2)	
Codigoro	50 (15.4)	83 (15.7)	
Copparo	20 (6.1)	31 (5.9)	
Ferrara	120 (36.8)	217 (41.1)	
Portomaggiore	23 (7.1)	51 (9.7)	
Missing	79 (24.2)	92 (17.4)	

^a T-test.

^b Chi-squared test

Note: All the comparison between groups were calculated for non-missing information.

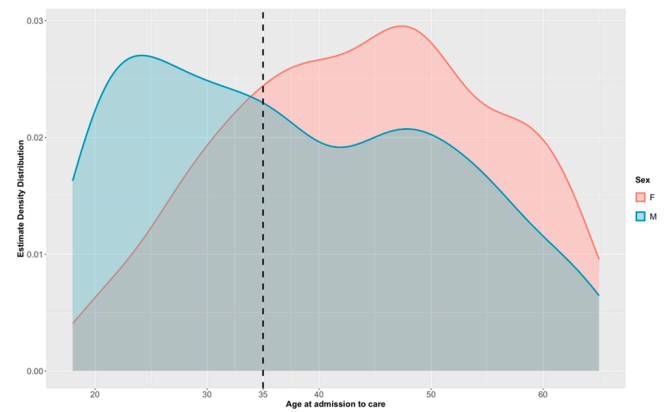


Fig. 1. Distribution of age at admission to care for FEP by sex. The black dashed vertical line is set at age 35 (upper age limit for admission to FEP services in Italy).

Consequently, more of those aged 36 and over were living with their own families or alone compared to the under-35s (28.8% vs 10.4%, $p < 0.01$; 10.8% vs 5.8%, $p < 0.01$); as expected, more ≤ 35s were living with their parents (34.3% vs 16.1%, $p < 0.01$). A higher proportion of patients in the under-35s group completed high school (31.0% vs 21.8%, $p < 0.01$) or university (10.4% vs 7.0%, $p < 0.01$) education, while more over-35s completed primary and middle school (6.0% vs 5.8%, $p < 0.01$; 25.8% vs 17.8%, $p < 0.01$), however many data regarding educational level is missing.

As shown in Table 2, the most common primary psychosis diagnosis in both groups was “Other non-organic psychoses”, making up 45.7% of ≤35s and 33.7% of 36+. Between the two groups, there was a similar proportion of schizophrenic psychoses (21.5% in under-35s vs 21.6% in over-35s). The proportions were almost the same for the last recorded primary diagnosis. The over-35s group were significantly more frequently diagnosed with “episodic mood disorders” (21.6% vs 13.5%, $p < 0.01$) and “delusional disorders” (22.2% vs 19.0%, $p < 0.01$). The last primary recorded diagnoses saw an increase of “schizophrenic psychoses” diagnoses while “other non-organic psychoses” and “delusional disorders” decreased compared to the first primary diagnosis. Of note, in the 36+ there was also 1.3% of patients with the last recorded

Table 2
Psychosis diagnoses by age group.

	≤ 35 N = 326 (38.2%)	36+ N = 528 (61.8%)	p-value
First Primary Psychosis Diagnosis, N (%)			<0.01 ^a
Schizophrenic psychoses (ICD-9 295.*)	70 (21.5)	114 (21.6)	
Episodic mood disorders (ICD-9 296.54; 296.14; 296.64; 296.44; 296.24; 296.34)	44 (13.5)	114 (21.6)	
Delusional disorders (ICD-9 297.*)	62 (19.0)	117 (22.2)	
Other non-organic psychoses (ICD-9 298.*)	149 (45.7)	178 (33.7)	
Unspecified psychoses (ICD- 9 299.90; 299.91)	1 (0.3)	5 (0.9)	
Last Primary recorded Diagnosis, N (%)			<0.01 ^a
Schizophrenic psychoses (ICD-9 295.*)	81 (24.9)	127 (24.0)	
Episodic mood disorders (ICD-9 296.54; 296.14; 296.64; 296.44; 296.24; 296.34)	47 (14.4)	113 (21.4)	
Delusional disorders (ICD-9 297.*)	54 (16.6)	110 (20.8)	
Other non-organic psychoses (ICD-9 298.*)	139 (42.6)	164 (31.1)	
Unspecified psychoses (ICD- 9 299.90; 299.91)	1 (0.3)	4 (0.8)	
Personality disorders (ICD-9 301.*)	3 (0.9)	3 (0.6)	
Mild mental retardation (ICD-9 317)	1 (0.3)	7 (1.3)	

^a Chi-squared test.

diagnosis of “mild mental retardation”, which was not present at admission, and 0.6% with a diagnosis of personality disorder.

At admission, “episodic mood disorders” were significantly more frequent in women compared to men (22.6% vs 9.1%, $p < 0.01$ in the ≤ 35 group), a finding that was confirmed also in the last recorded primary diagnosis (24.5% vs 9.5%, $p < 0.01$) (Table 3).

3.2. Service pathways to and through care

During the study period, the annual number treated among those aged 36 or more showed more variation over the years compared to that of those under-35s and was almost twice as high as the number treated among younger FEP (annual median 57 new cases vs 32) (see Supplementary Figure 1).

As detailed in Table 4, a higher proportion of patients under-35s compared to those aged 36+ were hospitalized (63.5% vs 47.2%, $p < 0.01$), and with higher frequency (mean 2.3 vs 1.7 hospitalization/person, $p < 0.01$). Antipsychotics were the psychotropic category most frequently prescribed in both groups, while long-acting injectables (LAI) was less frequently prescribed in the older group (6.3% vs 9.0%, $p = 0.36$). Antidepressants were more prescribed in those aged 36 and over (15.3% vs 8.0%, $p < 0.01$).

In the older group, somewhat higher proportions of women than men were hospitalized and prescribed medication (Table 5), but this difference was not statistically significant. Interestingly, women were less frequently prescribed LAI compared to men (1.7% vs 12.3% in under-35s, $p = 0.04$; 3.7% vs 10.0% in those aged 35 and over, $p = 0.07$) but were more frequently prescribed antidepressants (12.3% vs 5.9%, $p = 0.07$ in under-35s; 16.3% vs 14.1%, $p = 0.56$ in over-35s).

4. Discussion

Our findings showed that among patients aged between 18 and 65 years at their first access to CMHCs for FEP, most were aged 35 or more and that, in this group, the majority were women. This finding has two main implications from a public health perspective: first, it shows that the majority of FEP accessed community mental health services after age 35, thus identifying a potential area for early detection and treatment; second, while confirming the most current epidemiological evidence in literature that showed women having their FEP later in life (Sommer et al., 2023; Ferrara et al., 2023a; Jongasma et al. 2018), it underlines a possible inequity in treatment (Wierenga et al. 2023). In fact, current FEP services which maintain an upper age cut-off of 35 are excluding more women than men from specialized treatment. Our data replicates

Table 3
Diagnoses by age group and by sex.

	≤ 35 N = 326 (38.2%)		p-value	36+ N = 528 (61.8%)		p-value
	M N = 220 (67.5%)	F N = 106 (32.5%)		M N = 234 (44.3%)	F N = 294 (55.7%)	
First Primary Psychosis Diagnosis, N (%)						
Schizophrenic psychoses (ICD-9 295.*)	49 (22.3)	21 (19.8)	$<0.01^a$	63 (26.9)	51 (17.3)	0.10 ^a
Episodic mood disorders (ICD-9 296.54; 296.14; 296.64; 296.44; 296.24; 296.34)	20 (9.1)	24 (22.6)		45 (19.2)	69 (23.5)	
Delusional disorders (ICD-9 297.*)	48 (21.8)	14 (13.2)		52 (22.2)	65 (22.1)	
Other non-organic psychoses (ICD-9 298.*)	102 (46.4)	47 (44.4)		72 (30.8)	106 (36.1)	
Unspecified psychoses (ICD-9 299.90; 299.91)	1 (0.4)	0 (0.0)		2 (0.9)	3 (1.0)	
Last Primary recorded Diagnosis, N (%)						
Schizophrenic psychoses (ICD-9 295.*)	60 (27.3)	21 (19.8)	$<0.01^a$	64 (27.3)	63 (21.4)	0.57 ^a
Episodic mood disorders (ICD-9 296.54; 296.14; 296.64; 296.44; 296.24; 296.34)	21 (9.5)	26 (24.5)		45 (19.2)	68 (23.1)	
Delusional disorders (ICD-9 297.*)	40 (18.2)	14 (13.2)		52 (22.2)	58 (19.7)	
Other non-organic psychoses (ICD-9 298.*)	95 (43.2)	44 (41.5)		66 (28.2)	98 (33.3)	
Unspecified psychoses (ICD-9 299.90; 299.91)	1 (0.4)	0 (0.0)		2 (0.9)	2 (0.7)	
Personality disorders (ICD-9 301.*)	3 (1.4)	0 (0.0)		2 (0.9)	1 (0.4)	
Mild mental retardation (ICD-9 317)	0 (0.0)	1 (1.0)		3 (1.3)	4 (1.4)	

^aChi-squared test.

Table 4
Service pathways by age group.

	≤ 35 N = 326 (38.2%)	36+ N = 528 (61.8%)	p-value
Psychiatric inpatients hospitalizations, Yes, N (%)	207 (63.5)	249 (47.2)	$<0.01^a$
Number of inpatient hospitalizations*			$<0.01^b$
Mean (SD)	2.3 (3.0)	1.7 (2.9)	
Median (min; max)	1 (1; 23)	1 (1; 41)	
Prescribed at least one psychotropic medication, yes, N (%)	227 (69.6)	331 (62.7)	0.04 ^a
Number of psychotropic medications prescribed [^]			0.06 ^b
Mean (SD)	2.0 (1.0)	2.3 (1.3)	
Median (min; max)	2 (1; 6)	2 (1; 7)	
Type of medication prescribed, yes, N (%)			
Antipsychotic	189 (41.2)	270 (58.8)	0.06 ^a
Long Acting Injectable Antipsychotic	17 (9.0)	17 (6.3)	0.36
Antidepressant	26 (8.0)	81 (15.3)	<0.01
Mood stabilizer	16 (4.9)	36 (6.8)	0.32

* Calculated on those who had at least one hospitalization.

[^] Calculated on those with at least one pharmacological prescription.

[^] Calculated on those who had at least one antipsychotic prescribed.

^a Chi-squared test.

^b Mann-Whitney test.

two studies conducted in the UK (Jagger et al. 2020; Thakrar, Bardhan, and Chakraborty 2023) after NICE extended the upper age limit at 65 both for the increase in workload, and for the finding that women have a second peak of psychoses in their mid-late 40 s (Häfner et al. 1998; Cocchi et al. 2014; Ferrara et al. 2019; Ferrara et al., 2023a).

It is difficult to compare our study with similar studies in Italy, because it is the first of its kind for design and age range. In fact, only Lasalvia and collaborators, in 2012, investigated the characteristics of FEP users older than the usual patients admitted to EIP services in the Psychosis Incident Cohort Outcome Study (PICOS); however, the inclusion age range was 15–54, while in our study it was 18–65. Moreover, the PICOS’s study was conducted with a prospective longitudinal design (Lasalvia et al. 2012), while ours is retrospective. Later, in 2014, the same authors conducted an epidemiologically study within PICOS, with the aim to explore the role of socio-demographic risk factors for psychoses (Lasalvia et al. 2014). They reported that incidence rates were significantly higher for females in the 40–49 year age range and for males in the age range 15–19 years, and that women showed a higher incidence of affective psychosis than men.

Table 5
Service pathways by age group and by sex.

	≤ 35 N = 326%=38.2		p-value	36+ N = 528%=61.8		p-value
	M N = 220 (67.5%)	F N = 106 (32.5%)		M N = 234 (44.3%)	F N = 294 (55.7%)	
Psychiatric inpatient hospitalizations, Yes, N (%)	140 (63.6)	67 (63.2)	1 ^a	105 (44.9)	144 (49.0)	0.39 ^a
Number of inpatient hospitalizations [*]			0.32 ^b			0.33 ^b
Mean (SD)	2.4 (3.2)	2.1 (2.6)		1.8 (4.0)	1.6 (1.7)	
Median (min; max)	1 (1; 23)	1 (1; 18)		1 (1; 41)	1 (1; 16)	
Prescribed at least one psychotropic medication, yes, N (%)	152 (69.1)	75 (70.7)	0.85 ^a	139 (59.4)	192 (65.3)	0.19 ^a
Number of psychotropic medications prescribed [†]			0.91 ^b			0.14 ^b
Mean (SD)	2.1 (1.1)	2.0 (0.9)		2.4 (1.3)	2.2 (1.3)	
Median (min; max)	2 (1; 6)	2 (1; 4)		2 (1; 7)	2 (1; 7)	
Type of medication prescribed, yes, N (%)						
Antipsychotic	130 (59.1)	59 (55.6)	0.63 ^a	110 (47.0)	160 (54.4)	0.11 ^a
Long Acting Injectable Antipsychotic			0.04 ^a			
	16 (12.3)	1 (1.7)		11 (10.0)	6 (3.7)	0.07 ^a
Antidepressant	13 (5.9)	13 (12.3)	0.07 ^a	33 (14.1)	48 (16.3)	0.56 ^a
Mood stabilizer	8 (3.6)	8 (7.5)	0.21 ^a	20 (8.5)	16 (5.4)	0.21 ^a

* Calculated on those who had at least one hospitalization.

† Calculated on those with at least one pharmacological prescription.

[^] Calculated on those who had at least one antipsychotic prescribed.

^a Chi-squared test.

^b Mann-Whitney test.

As expected, in our study, most of under-35s were single and living with their parents, while there were more married people in the older group and, consequently, more patients living with their own families. This finding has implications for care planning and caregivers' roles: by living with their parents, younger patients have limited housekeeping responsibilities and roles as income earners. Moreover, the role of parents as caregivers is strategic for the care planning, as professionals could rely on them for supervision and help during the recovery process (Cascio et al. 2012). On the contrary, older patients in our study were usually married and living with their acquired family: thus, we could hypothesize that they hold more stringent household and possibly parenting responsibilities. This is particularly true if we consider that in our sample older patients were predominantly women, who are usually the designated caregivers of children or vulnerable adults, and responsible for housekeeping (Ferrara et al., 2023a; Seeman 2019).

Of note, one in ten of over-35s patients were separated, divorced, or widowed and living alone: in this case, it may be necessary to rely on offspring, if they are capable and old enough to become caregivers themselves. This possibility rises challenges related to the needs to involve young adults, sometimes even teenagers, in their parents' care process. It may be necessary to rethink psychoeducational and support interventions for the young caregivers, considering more specific tools. This change in the family setting compared to younger FEP is also reported by Thakrar et al. (2023) prior to 2016, carers' psychoeducation groups were mainly formed by parents of children attending school or university and only sometimes included spouses of young adults (in their 20 s or early 30 s), while with the new inclusion criteria groups included parents, spouses and children of patients in their 40 s and 50 s.

In the hypothesis of services oriented to older FEP it might be useful to envision the implementation of parenting training for patients who are also parents, who struggle to communicate news about their mental disorders to their children and might need external support navigating their role as a parent while also managing their mental illness (Nicholson and Henry 2003). Finally, FEP service providing care to those older than 35 should also envision the need for care of young children of the over 35 FEP, who are often sole parents. In fact, patients' young children not only can they not provide adequate support for their ill parent, but they might be themselves, in severe need of support and, perhaps, of active treatment (Apter et al. 2017). Not to mention the fact that children of parents with severe mental illness are at high risk themselves for developing emotional, behavioral, cognitive, and

psychiatric difficulties (Ranning et al. 2019) for both genetic and epigenetic reasons (i.e., exposure to early life adversities) (Jami et al. 2021; Cowan et al. 2016), and thus psychiatric services might provide preventive interventions (Lannes et al. 2021), and an adequate monitoring for their mental health (Arango et al. 2018; Goodyear et al. 2015).

The diagnoses of "episodic mood disorders" were mostly reported in those aged 35 or over and in women (Pallier et al. 2022; Pence et al. 2022): this finding is concordant with that of other studies (Clay et al. 2018; Jagger et al. 2020; O'Driscoll et al. 2021; Selvendra et al. 2014b; Lasalvia et al. 2014). It must be considered that affective symptoms may interfere with illness trajectory by negatively affecting recovery (Van Eck et al. 2018) so it may be useful to adopt specific therapeutic techniques with a special focus on mood (Arrasate et al. 2016).

Our findings show a more pronounced variation in the number of new FEP cases over time above the age of 35, and a higher prevalence of older FEP compared to younger. This highlights that if FEP age criteria were to be lifted, a workforce implementation might need to be put in place given the increase in workload in order to provide the high quality and high intensity treatment that characterizes the FEP services. In addition, as other authors have pointed out (Greenfield et al. 2018; Adamson et al. 2018), it is important to rethink the structure of EIP services and tailor interventions for the older patients, because of the greater complexity they introduce. They bear social needs different from those of youth, for example they are more likely to have child dependents and financial obligations: a stronger connection with social services would be needed, and psychosocial interventions whose aim is to help the older patient returning to work (O'Driscoll et al. 2021). It would also be necessary to have a more direct liaison with physical medicine (Severi et al. 2018), because of more frequent metabolic disorders (Selvendra et al. 2014b), especially considering that people with psychosis have worse physical health and a lower life expectancy than the general population (Laursen, Munk-Olsen, and Vestergaard 2012; Stubbs et al. 2016). It is important also to consider a possible liaison with obstetrics and gynecology services, considering that the majority of patients over 35 are women and the role that oscillating hormones play during a women life's stages in physical and mental health (Ferrara et al. 2024; Ferrara and Srihari 2021; Sommer et al. 2023). Hospitalization was more frequent in younger adults: this result might reflect the clinical characteristics of younger male FEP, whose onset might be complicated by aggressive and disorganized behavior, often associated to substance abuse or intoxication that leads to hospitalization.

The pharmacological treatment differed between the two age groups, in fact LAI were more often prescribed to younger FEP and less often prescribed to women, and older FEP were more often prescribed antidepressants: this finding is comparable to those of other studies

(Sommer et al., 2023; Ferrara et al., 2023a) and it might be attributed to the bias of professionals who offer LAI to less compliant patients and think women and older individuals are more compliant with pharmacological prescriptions, but the available literature does not support this (Santos-Casado and Garcia-Avello 2019; Zhou et al. 2016) (Oehl, Hummer, and Fleischhacker 2000; Taylor and Bragado-Jimenez 2009). These data might be useful for quality improvement initiatives, such as educational activities to modify possible bias and promote a more equitable offering of LAI, which in various studies proved to be more effective than oral medications in preventing hospitalizations and relapses (Kishimoto et al. 2021; Ceraso et al. 2020; Stahl 2014).

Our findings must be interpreted in light of some limitations. First, this is a retrospective study, thus it is possible that some data are missing from the dataset and might have influenced the results, notably for marital status, education level, and living conditions. However, all the comparison between groups were calculated for non-missing information only. Second, the sample size is limited to a defined geographical catchment, with specific socio-economic characteristics. However, our main findings align with those of the most current UK and available Italian literature, thus we think our results can be generalizable to similar FEP services in western Europe. Third, information regarding referrer, medical comorbidities, duration of untreated psychosis, and severity of illness (Ferrara et al., 2023b), that might have affected their presentation to the services, are not included in the dataset, and this limits the interpretation of our results.

5. Conclusion

This study, being the first epidemiological report of treated incidence of FEP up to age 65 in Italy, provides numerous insights of the socio-demographic and clinical differences based on age: these findings allow to considerations for service planning and a possible evolution of FEP service from youth-oriented services to a more holistic program.

This poses numerous challenges for all stakeholders, but it might represent an opportunity for quality improvement initiatives, that would promote tailored approach based on age, sex, gender role, and care needs.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Derived data supporting the findings of this study are available from the corresponding author [MF] on request.

CRediT authorship contribution statement

Maria Ferrara: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Ilaria Domenicano:** Data curation, Formal analysis. **Aurora Marchi:** Formal analysis, Writing – original draft. **Giulia Zaffarini:** Writing – review & editing. **Alice Onofrio:** Writing – review & editing. **Lorenzo Benini:** Data curation, Software. **Cristina Sorio:** Supervision. **Elisabetta Gentili:** Software, Data curation. **Martino Belvederi Murri:** Supervision. **Tommaso Toffanin:** Supervision. **Julian Little:** Supervision. **Luigi Grassi:** Supervision.

Declaration of competing interest

None

Acknowledgments

Julian Little holds a Distinguished Research Chair in Chronic Disease Epidemiology and Control from the University of Ottawa.

This work was supported by NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022) (M.F., M.B.M., T.T., L.G.)

E.G. was supported by a scholarship financed by the Ministerial Decree no. 351 of 9th April 2022, based on the NRRP - funded by the European Union - NextGenerationEU - Mission 4 “Education and Research”, Component 1 “Enhancement of the offer of educational services: from nurseries to universities” - Investment 4.1 “Extension of the number of research doctorates and innovative doctorates for public administration and cultural heritage” while attending the PhD programme in Engineering Science at the University of Ferrara, Cycle XXXVIII.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116034.

References

- Adamson, V., Barrass, E., McConville, S., Irikok, C., Taylor, K., Pitt, S., Van Duyn, R., Bennett, S., Jackson, L., Carroll, J., Andrews, M., Parker, A., Wright, C., Greethead, K., Price, D., 2018. 'Implementing the access and waiting time standard for early intervention in psychosis in the United Kingdom: an evaluation of referrals and post-assessment outcomes over the first year of operation. *Early. Interv. Psychiatry* 12, 979–986.
- Apter, G., Bobin, A., Genet, M.C., Gratier, M., Devouche, E., 2017. Update on mental health of infants and children of parents affected with mental health issues. *Curr. Psychiatry Rep.* 19, 72.
- Arango, C., Diaz-Caneja, C.M., McGorry, P.D., Rapoport, J., Sommer, I.E., Vorstman, J. A., McDavid, D., Marin, O., Serrano-Drozdzowskyj, E., Freedman, R., Carpenter, W., 2018. Preventive strategies for mental health. *Lancet Psychiatry* 5, 591–604.
- Arrasate, M., González-Ortega, I., García-Alocén, A., Alberich, S., Zorrilla, I., González-Pinto, A., 2016. Prognostic value of affective symptoms in first-admission psychotic patients. *Int. J. Mol. Sci.* 17, 1039.
- Belvederi Murri, M., Bertelli, R., Carozza, P., Berardi, L., Cantarelli, L., Croce, E., Antenora, F., Curtarello, E.M.A., Simonelli, G., Recla, E., Girotto, B., Grassi, L., Psychosis Ferrara Working Group on First-Episode, and Idmhpa coordinating team Ferrara Working Group on First-Episode Psychosis in Ferrara includes, 2021. 'First-episode psychosis in the Ferrara mental health department: incidence and clinical course within the first 2 years. *Early. Interv. Psychiatry* 15, 1738–1748.
- Belvederi Murri, M., Ferrara, M., Imbesi, M., Leuci, E., Marchi, M., Musella, V., Natali, A., Neri, A., Ragni, S., Saponaro, A., Tarricone, I., Tullini, A., Starace, F., Group Early Psychosis Working, 2023. A public early intervention approach to first-episode psychosis: treated incidence over 7 years in the Emilia-Romagna region. *Early. Interv. Psychiatry*.
- Breithorpe, N.J., Srihari, V.H., Woods, S.W., 2009a. Review of the operational definition for first-episode psychosis. *Early. Interv. Psychiatry* 3, 259–265.
- . 2009b. 'Review of the operational definition for first-episode psychosis', *Early. Interv. Psychiatry*, 3.
- Cascio, M.T., Cella, M., Preti, A., Meneghelli, A., Cocchi, A., 2012. 'Gender and duration of untreated psychosis: a systematic review and meta-analysis. *Early. Interv. Psychiatry* 6.
- Ceraso, A., Lin, J.J., Schneider-Thoma, J., Sifias, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Davis, J.M., Leucht, S., 2020. Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst. Rev.* 8.
- Challis, S., Nielssen, O., Harris, A., Large, M., 2013. Systematic meta-analysis of the risk factors for deliberate self-harm before and after treatment for first-episode psychosis. *Acta Psychiatr. Scand.* 127, 442–454.
- Clay, F., Allan, S., Lai, S., Laverty, S., Jagger, G., Treise, C., Perez, J., 2018. The over-35s: early intervention in psychosis services entering uncharted territory. *BJPsych. Bull.* 42.
- Cocchi, A., Lora, A., Meneghelli, A., Greca, E.La, Pisano, A., Cascio, M.T., Preti, A., 2014. Sex differences in first-episode psychosis and in people at ultra-high risk. *Psychiatry Res.* 215.
- Correll, C.U., Galling, B., Pawar, A., Krivko, A., Bonetto, C., Ruggeri, M., Craig, T.J., Nordentoft, M., Srihari, V.H., Guloksuz, S., Hui, C.L.M., Chen, E.Y.H., Valencia, M., Juarez, F., Robinson, D.G., Schooler, N.R., Brunette, M.F., Mueser, K.T., Rosenheck, R.A., Marcy, P., Addington, J., Estroff, S.E., Robinson, J., Penn, D., Severe, J.B., Kane, J.M., 2018. 'Comparison of early intervention services vs treatment as usual for early-phase psychosis: a systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry* 75, 555–565.

- Cowan, C.S.M., Callaghan, B.L., Kan, J.M., Richardson, R., 2016. The lasting impact of early-life adversity on individuals and their descendants: potential mechanisms and hope for intervention. *Genes, Brain Behavior* 15, 155–168.
- de Girolamo, G., Dagani, G., Purcell, R., Cocchi, A., McGorry, P.D., 2012. Age of onset of mental disorders and use of mental health services: needs, opportunities and obstacles. *Epidemiol. Psychiatr. Sci.* 21.
- De Girolamo, G., 2008. The Italian guidelines for early intervention in schizophrenia: development and conclusions. *Early. Interv. Psychiatry* 2, 291–302.
- Ferrara, M., Curtarello, E.M.A., Gentili, E., Domenicano, I., Vecchioni, L., Zese, R., Alberti, M., Franchini, G., Sorio, C., Benini, L., Little, J., Carozza, P., Dazzan, P., Grassi, L., 2023a. Sex differences in schizophrenia-spectrum diagnoses: results from a 30-year health record registry. *Arch. Womens Ment. Health*.
- Ferrara, M., Gentili, E., Belvederi Murri, M., Zese, R., Alberti, M., Franchini, G., Domenicano, I., Folesani, F., Sorio, C., Benini, L., Carozza, P., Little, J., Grassi, L., 2023b. Establishment of a public mental health database for research purposes in the Ferrara province: development and preliminary evaluation study. *JMIR. Med. Inform.* 11.
- Ferrara, M., Srihari, V.H., 2021. Early Intervention for Psychosis in the United States: tailoring Services to Improve Care for Women. *Psychiatr. Serv.* 72.
- Ferrara, M., Tedeschini, E., Baccari, F., Musella, V., Vacca, F., Mazzi, F., Ferri, M., Srihari, V., Starace, F., Group Early Psychosis Working, 2019. Early intervention service for first episode psychosis in Modena, Northern Italy: the first hundred cases. *Early. Interv. Psychiatry* 13, 1011–1017.
- Ferrara, Maria, Panzani, Anna, Macis, Giulia, Sorio, Cristina, Domenicano, Ilaria, Muscettola, Angela, Carozza, Paola, Grassi, Luigi, 2024. Women and mental health: a gender-sensitive survey on determinants of health and care satisfaction in outpatient psychiatric services. *J. Sex Gender-Specific Med.* 10, 12–22.
- Fusar-Poli, P., McGorry, P.D., Kane, J.M., 2017. Improving outcomes of first-episode psychosis: an overview. *World Psychiatry: Official J. World Psychiatric Association (WPA)* 16.
- Goodyear, Melinda, Hill, Terri-Lee, Allchin, Becca, McCormick, Francis, Hine, Rochelle, Cuff, Rose, O'Hanlon, Brendan, 2015. Standards of practice for the adult mental health workforce: meeting the needs of families where a parent has a mental illness. *Int. J. Ment. Health Nurs.* 24, 169–180.
- Greenfield, P., Joshi, S., Christian, S., Lekkos, P., Gregorowicz, A., Fisher, H.L., Johnson, S., 2018. First episode psychosis in the over 35 s: is there a role for early intervention? *Early. Interv. Psychiatry* 12, 348–354.
- Gruppo di lavoro Esordi Psicotici, R. E. R., 2016. Raccomandazioni Regionali Per La Promozione Della Salute e Del Benessere in Persone All'esordio Psicotico. Centro Stampa della Regione Emilia-Romagna, Bologna.
- Häfner, H., an der Heiden, W., Behrens, S., Gattaz, W.F., Hambrecht, M., Löffler, W., Maurer, K., Munk-Jørgensen, P., Nowotny, B., Riecher-Rössler, A., Stein, A., 1998. Causes and consequences of the gender difference in age at onset of schizophrenia. *Schizophr. Bull.* 24.
- Jagger, G., de la Fuente-Tomas, L., Stochl, J., Allan, S.M., Clay, F., Keneder, L., Treise, C., Perez, J., 2020. Early intervention in psychosis treatment components utilization in patients aged over 35'. *Community Ment. Health J.* 56.
- Jami, Eshim S., Hammerschlag, Anke R., Bartels, Meike, Middeldorp, Christel M., 2021. Parental characteristics and offspring mental health and related outcomes: a systematic review of genetically informative literature. *Trans. Psychiatry* 11, 197.
- Jongsma, H.E., Gayer-Anderson, C., Lasalvia, A., Quattrone, D., Mule, A., Szoke, A., Selten, J.P., Turner, C., Arango, C., Tarricone, I., Berardi, D., Tortelli, A., Llorca, P. M., de Haan, L., Bobes, J., Bernardo, M., Sanjuan, J., Santos, J.L., Arrojo, M., Del-Ben, C.M., Menezes, P.R., Velthorst, E., Murray, R.M., Rutten, B.P., Jones, P.B., van Os, J., Morgan, C., Kirkbride, J.B., Group European Network of National Schizophrenia Networks Studying Gene-Environment Interactions Work Package, 2018. Treated incidence of psychotic disorders in the multinational EU-GEI study. *JAMA Psychiatry* 75, 36–46.
- Kirkbride, J.B., Erazuriz, A., Croudace, T.J., Morgan, C., Jackson, D., Boydell, J., Murray, R.M., Jones, P.B., 2012. Incidence of schizophrenia and other psychoses in England, 1950–2009: a systematic review and meta-analyses. *PLoS. One* 7.
- Kishimoto, T., Hagi, K., Kurokawa, S., Kane, J.M., Correll, C.U., 2021. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-study studies. *Lancet. Psychiatry* 8.
- Lannes, Alice, Bui, Eric, Arnaud, Catherine, Raynaud, Jean-Philippe, Revet, Alexis, 2021. Preventive interventions in offspring of parents with mental illness: a systematic review and meta-analysis of randomized controlled trials. *Psychol. Med.* 51, 2321–2336.
- Large, M.M., Nielsens, O., 2011. Violence in first-episode psychosis: a systematic review and meta-analysis. *Schizophr. Res.* 125.
- Lasalvia, A., Bonetto, C., Tosato, S., Zanatta, G., Cristofalo, D., Salazzari, D., Lazzarotto, L., Bertani, M., Bissoli, S., De Santi, K., Cremonese, C., De Rossi, M., Gardellini, F., Ramon, L., Zucchetto, M., Amaddeo, F., Tansella, M., Ruggeri, M., Brambilla, P., Marrella, G., Perlini, C., Tito, P., Lunardon, M., Gava, F., Borso, E., Grandina, L., Paliotto, M., Roggia, L., Danielli, A., Poloni, C., Altiero, M.R., Piazza, F., Ceccato, E., Busana, C., Campi, A., Zancanato, A., Zamorani, P., Binotto, R., Caneva, A., Lazzarin, E., Zordan, G., Dolce, C., Fanchin, G.B., Negro, C., Gardellini, F., Crestale, M., Paiola, L., Sale, A., Morandini, I., Biondi, E., Cordella, A., Favaretto, G., Geatti, S., Urbani, P., De Rossi, M., Zanatta, G., Spessotto, J., Penelope, R., Grando, L., Sgnaolin, M., Tozzini, C., Visentin, G., Schiavon, L., Gentile, B., Bolacchi, M.G., Marzotto, L., Moni, F., Rossi, L., Amalric, I., Miceli, C., De Zordo, M. R., Ramon, L., Russo, S., Rossi, R., Casagrande, G., De Nardo, V., Facchetti, A., Ramaciotti, F., Marangon, V., Coppola, G., Marcolin, A., Meneghini, P., Sbraccia, F., Segato, C., Riolo, R., Cappellari, L., Cutugno, M., Meneghetti, L., Longhin, L., Paoleschi, B., Scalabrin, D., Antonello, L., Purgato, A., Santucci, G., Tosin, C., Volpato, R., Zurlo, R., Zucchetto, M., Pedron, M., Pinton, S., Benetazzo, M., Cremonese, C., Pavan, L., Semenzin, M., Sifari, L., Zorzi, F., Martucci, M.M., Magno, N., Meloni, G., Toniolo, E., Pavanati, M., Destro, E., Finotti, L., Florio, R., Marsilio, A., Pedrocchi, N., Pollola, P., Lazzarotto, L., Nosè, F., Rossin, P., Vivenza, V., Lasalvia, A., Bertani, M., Bissoli, S., De Santi, K., Marrella, G., Mazzoncini, R., Ruggeri, M., Urbani, A., Bianchi, L., Carcereri, G., Lunardi, L., Migliorini, G., Perdoná, G., Piazza, C., La Monaca, D., D'Agostini, G., Boggian, I., Piccione, G., Saladini, E., Gomez, F., Frazzinaro, S., Nicolaou, S., Cordioli, L., Bertolazzi, G., Pagliuca, V., Abate, M., Bortolomasi, M., Giacopuzzi, M., Segala, M., De Nardi, F., Bassetto, F., Bernardis, C., Bezzetto, A., Santi, M., 2014. 'First-contact incidence of psychosis in north-eastern Italy: influence of age, gender, immigration and socioeconomic deprivation. *Br. J. Psychiatry* 205, 127–134.
- Lasalvia, A., Tosato, S., Brambilla, P., Bertani, M., Bonetto, C., Cristofalo, D., Bissoli, S., De Santi, K., Lazzarotto, L., Zanatta, G., Marrella, G., Mazzoncini, R., Zanoni, M., Garzotto, N., Dolce, C., Nicolau, S., Perlini, C., Rambaldelli, G., Bellani, M., Tansella, M., Ruggeri, M., Group, PICOS-Veneto, 2012. Psychosis incident cohort outcome study (PICOS): a multisite study of clinical, social and biological characteristics, patterns of care and predictors of outcome in first-episode psychosis. background, methodology and overview of the patient sample. *Epidemiol. Psychiatr. Sci.* 21.
- Laursen, T.M., Munk-Olsen, T., Vestergaard, M., 2012. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Curr. Opin. Psychiatry* 25.
- Marshall, M., Husain, N., Bork, N., Chaudhry, I.B., Lester, H., Everard, L., Singh, S.P., Freemantle, N., Sharma, V., Jones, P.B., Fowler, D., Amos, T., Tomenson, B., Birchwood, M., 2014. Impact of early intervention services on duration of untreated psychosis: data from the National EDEN prospective cohort study. *Schizophr. Res.* 159.
- McGorry, P.D., 2007. The specialist youth mental health model: strengthening the weakest link in the public mental health system. *Med. J. Aust.* 187, S53–S56.
- McGorry, P.D., Killackey, E., Yung, A.R., 2007. Early intervention in psychotic disorders: detection and treatment of the first episode and the critical early stages. *Med. J. Aust.* 187.
- Meneghelli, A., Ciancaglini, P., Di Domenico, M., Mazzola, A., Ghio, L., Preti, A., 2023. Implementation of early intervention clinical services within the National Health System in Italy: third wave survey with focus on structures, resources, and fidelity to the evidence-based model. *Early. Interv. Psychiatry*.
- National Institute for Health Care Excellence, 2016. Implementing the Early Intervention in Psychosis Access and Waiting Time Standard: Guidance. NHS England Publication, London.
- Nicholson, J., Henry, A.D., 2003. Achieving the goal of evidence-based psychiatric rehabilitation practices for mothers with mental illnesses. *Psychiatr. Rehabil. J.* 27.
- O'Driscoll, C., Free, K., Attard, A., Carter, P., Mason, J., Shaikh, M., 2021. Transitioning to age inclusive early intervention for psychosis. *Early. Interv. Psychiatry* 15.
- Oehl, M., Hummer, M., Fleischhacker, W.W., 2000. Compliance with antipsychotic treatment. *Acta psychiatrica Scandinavica. Supplementum*.
- Pallier, P.N., Ferrara, M., Romagnolo, F., Ferretti, M.T., Soreq, H., Cerase, A., 2022. Chromosomal and environmental contributions to sex differences in the vulnerability to neurological and neuropsychiatric disorders: implications for therapeutic interventions. *Prog. Neurobiol.* 219.
- Parzen, Emanuel., 1962. On Estimation of a probability density function and mode. *Ann. Math. Stat.* 33, 1065–1076, 12.
- Pence, A.Y., Pries, L.K., Ferrara, M., Rutten, B.P.F., van Os, J., Guloksuz, S., 2022. Gender differences in the association between environment and psychosis. *Schizophr. Res.* 243.
- Penttilä, M., Jaaskelainen, E., Hirvonen, N., Isohanni, M., Miettunen, J., 2014. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br. J. Psychiatry* 205, 88–94.
- Pollard, J.M., Ferrara, M., Lin, I.H., Kucukgoncu, S., Wasser, T., Li, F., Srihari, V.H., 2020. Analysis of early intervention services on adult judicial outcomes. *JAMA Psychiatry* 77.
- Pollard, Jessica, Cahill, John, Srihari, Vinod, 2016. Building early intervention services for psychotic disorders: a primer for early adopters in the U.S'. *Curr. Psychiatry Rev.* 12, 350–356.
- Power, P., 2019. Early intervention services for psychosis in Ireland: are we there yet? *Ir. J. Psychol. Med.* 36, 243–248.
- Ranning, Anne, Benros, Michael E., Thorup, Anne A E, Davidsen, Kirstine Agnete, Hjorthøj, Carsten, Nordentoft, Merete, Laursen, Thomas Munk, Sørensen, Holger, 2019. Morbidity and mortality in the children and young adult offspring of parents with schizophrenia or affective disorders—a nationwide register-based cohort study in 2 million individuals'. *Schizophr. Bull.* 46, 130–139.
- Rosenblatt, Murray., 1956. Remarks on some nonparametric estimates of a density function. *Ann. Math. Stat.* 27, 832–837, 6.
- Santos-Casado, M., Garcia-Avello, A., 2019. Systematic review of gender bias in the clinical trials of new long-acting antipsychotic drugs. *J. Clin. Psychopharmacol.* 39, 264–272.
- Seeman, M.V., 2019. Does gender influence outcome in schizophrenia? *Psychiatr. Q.* 90.
- Selvendra, A., Baetens, D., Trauer, T., Petrakis, M., Castle, D., 2014a. First episode psychosis in an adult area mental health service—a closer look at early and late-onset first episode psychosis. *Australas. Psychiatry* 22, 235–241.
- . 2014b. 'First episode psychosis in an adult area mental health service—a closer look at early and late-onset first episode psychosis', *Australasian Psychiatry: bulletin of Royal Australian and New Zealand College of Psychiatrists*, 22.
- Severi, E., Ferrara, M., Tedeschini, E., Vacca, F., Mungai, F., Amendolara, R., Baccari, F., Starace, F., 2018. Assessment of cardiovascular risk in an Italian psychiatric

- outpatient sample: a chart review of patients treated with second-generation antipsychotics. *Int. J. Ment. Health Nurs.* 27, 1002–1008.
- Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J.B., Jones, P., Kim, J.H., Kim, J.Y., Carvalho, A.F., Seeman, M.V., Correll, C.U., Fusar-Poli, P., 2022. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. *Mol. Psychiatry* 27, 281–295.
- Sommer, I.E., Brand, B.A., Gangadin, S., et al., 2023. Women with Schizophrenia-Spectrum disorders after menopause: a vulnerable group for relapse. *Schizophr. Bull.* 49 (1), 136–143. <https://doi.org/10.1093/schbul/sbac139>.
- Srihari, Vinod H., Ferrara, Maria, Li, Fangyong, Kline, Emily, Gülöksüz, Sinan, Pollard, Jessica M., Cahill, John D., Mathis, Walter S., Sykes, Laura Yoviene, Walsh, Barbara C., 2022. Reducing the duration of untreated psychosis (dup) in a US community: a quasi-experimental trial. *Schizophr. Bull. Open* 3, sgab057.
- Stahl, S.M., 2014. Long-acting injectable antipsychotics: shall the last be first? *CNS Spectr.* 19.
- Stubbs, B., Koyanagi, A., Veronese, N., Vancampfort, D., Solmi, M., Gaughran, F., Carvalho, A.F., Lally, J., Mitchell, A.J., Mugisha, J., Correll, C.U., 2016. Physical multimorbidity and psychosis: comprehensive cross sectional analysis including 242,952 people across 48 low- and middle-income countries. *BMC Med.* 14.
- Taylor, P.J., Bragado-Jimenez, M.D., 2009. Women, psychosis and violence. *Int. J. Law Psychiatry* 32.
- Thakrar, V., Bardhan, M., Chakraborty, N., 2023. Early intervention in psychosis: an analysis of the characteristics and service needs of patients over the age of 35. *Early Interv Psychia.* 17 <https://doi.org/10.1111/eip.13318>.
- Van Eck, R.M., Burger, T.J., Vellinga, A., Schirmbeck, F., de Haan, L., 2018. The relationship between clinical and personal recovery in patients with schizophrenia spectrum disorders: a systematic review and meta-analysis. *Schizophr. Bull.* 44, 631–642.
- Wierenga, Lara Marise, Ruigrok, Amber, Aksnes, Eira Ranheim, Barth, Claudia, Beck, Dani, Burke, Sarah, Crestol, Arielle, Drunen, Lina van, Ferrara, Maria, Galea, Liisa Ann Margaret, Goddings, Anne-Lise, Hausmann, Markus, Homanen, Inka, Klinge, Ineke, Lange, Ann-Marie de, Ouwerkerk, Lieke, Miesen, Anna van der, Proppert, Ricarda, Rieble, Carlotta, Tamnes, Christian Krog, Bos, Marieke Geerte Nynke, 2023. Recommendations for a better understanding of sex and gender in neuroscience of mental health. *Biol. Psychiatry Glob. Open. Sci.*, 100283.
- Zhou, Jiansong, Xiang, Yu-Tao, Li, Qiguang, Zhu, Xiaomin, Li, Wen, Ungvari, Gabor S., Ng, Chee H., Ongur, Dost, Wang, Xiaoping, 2016. Gender differences in attitudes towards antipsychotic medications in patients with schizophrenia. *Psychiatry Res.* 245, 276–281.