CNS Spectrums

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Original Research

Cite this article: Fountoulakis KN, Dragioti E, Theofilidis AT, Wiklund T, Atmatzidis X, Nimatoudis I, Thys E, Wampers M, Hranov L, Hristova T, Aptalidis D, Milev R, Iftene F, Spaniel F, Knytl P, Furstova P, From T, Karlsson H, Walta M, Salokangas RKR, Azorin J-M, Bouniard J, Montant J, Juckel G, Haussleiter IS, Douzenis A, Michopoulos I, Ferentinos P, Smyrnis N, Mantonakis L, Nemes Z, Gonda X, Vajda D, Juhasz A, Shrivastava A, Waddington J, Pompili M, Comparelli A, Corigliano V, Rancans E, Navickas A, Hilbig J, Bukelskis L, Stevovic LI, Vodopic S, Esan O, Oladele O, Osunbote C, Rybakowski JK, Wojciak P, Domowicz K, Figueira ML, Linhares L, Crawford J, Panfil A-L, Smirnova D, Izmailova O, Lecic-Tosevski D, Temmingh H, Howells F, Bobes J, Garcia-Portilla MP, García-Alvarez L, Erzin G, Karadağ H, De Sousa A, Bendre A, Hoschl C, Bredicean C, Papava I, Vukovic O, Pejuskovic B, Russell V, Athanasiadis L, Konsta A, Fountoulakis NK, Stein D, Berk M, Dean O, Tandon R, Kasper S, and De Hert M (2022). Gender, age at onset, and duration of being ill as predictors for the long-term course and outcome of schizophrenia: an international multicenter study. *CNS Spectrums* **27**(6), 716–723.
https://doi.org/10.1017/S1092852921000742

Received: 18 March 2021
Accepted: 07 July 2021

Key words:
Gender; age at onset; duration; long-term course; outcome; schizophrenia

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Gender, age at onset, and duration of being ill as predictors for the long-term course and outcome of schizophrenia: an international multicenter study

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Abstract

Background. The aim of the current study was to explore the effect of gender, age at onset, and duration on the long-term course of schizophrenia.

Methods. Twenty-nine centers from 25 countries representing all continents participated in the study that included 2358 patients aged 37.21 ± 11.87 years with a DSM-IV or DSM-5 diagnosis of schizophrenia; the Positive and Negative Syndrome Scale as well as relevant clinicodemographic data were gathered. Analysis of variance and analysis of covariance were used, and the methodology corrected for the presence of potentially confounding effects.

Results. There was a 3-year later age at onset for females ($P < .001$) and lower rates of negative symptoms ($P < .01$) and higher depression/anxiety measures ($P < .05$) at some stages. The age at onset manifested a distribution with a single peak for both genders with a tendency of patients with younger onset having slower advancement through illness stages ($P = .001$). No significant effects were found concerning duration of illness.

Discussion. Our results confirmed a later onset and a possibly more benign course and outcome in females. Age at onset manifested a single peak in both genders, and surprisingly, earlier onset was related to a slower progression of the illness. No effect of duration has been detected. These results are partially in accord with the literature, but they also differ as a consequence of the different starting point of our methodology (a novel staging model), which in our opinion precluded the impact of confounding effects. Future research should focus on the therapeutic policy and implications of these results in more representative samples.

Significant Outcomes

- Females might manifest schizophrenia 3 years later in comparison to males.
- Females manifested lower rates of negative symptoms and higher depression/anxiety.
- The age at onset manifested a single peak for both genders.

Limitations of the Current Study

- The study utilized a cross-sectional design with the utilization of limited demographic and clinical information or treatment resistance status of the patients, and these were combined with lack of long-term follow-up of patients.
- A second limitation is that the study sample was not epidemiologically selected and therefore may not represent the general population of patients with schizophrenia. Instead, it represents those patients with at least less than ideal remission who remained in contact with mental health services for several years.

Introduction

Schizophrenia is a disorder with significant clinical heterogeneity, which could be the result of different causative factors, or alternatively could be due to innate constitutional differences among people, including the potential to manifest the symptomatology during different developmental stages. Many authors attribute this to differences in the age at onset as well as in the effect of gender.

In this frame, there is the debate whether schizophrenia is a purely neurodevelopmental disease, or whether a neuroprogressive component exists. Additional issues that theories so far failed to explain are the age and developmental stage at onset, the frequently episodic nature, and the long-term course and the variable outcome.

Recently, a staging method has been proposed,[1,2] and its main contribution is that it proposes the presence of four main stages of illness progress, with a specific aspect of symptomatology being dominant at each stage (Figure 1). This model is identical for both genders. The factors describing the model differ from the original Positive and Negative Syndrome Scale (PANSS) factors in their item composition. Therefore, and in order to avoid confusion, the

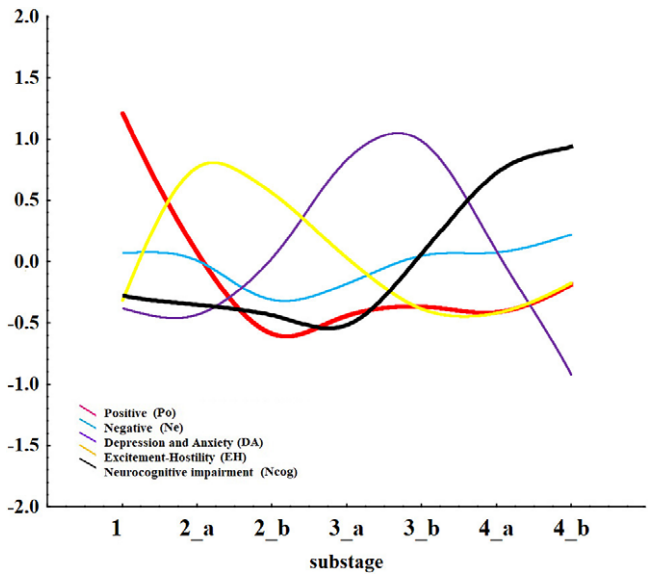

Figure 1. Plot of factor scores (*y*-axis) vs stages and substages of illness progression. *Notes:* Po: Positive symptoms factor according to the model dimensions. Ne: Negative symptoms factor according to the model dimensions. EH: Excitement-hostility symptoms factor according to the model dimensions. DA: Depression and anxiety symptoms factor according to the model dimensions. Ncog: Neurocognitive deficit factor according to the model dimensions. The above factors come from an analysis previously published,[1] and they do not correspond to classic PANNS subscales.

https://doi.org/10.1017/S1092852921000742 Published online by Cambridge University Press

new factors were named Po (instead of P), Ne (instead of N), EH (for excitation/hostility), DA (reflecting aspects of general psychopathology [GP] but especially depression and anxiety), and Ncog (reflecting neurocognitive impairment). This model clarifies the complex interaction between duration and clinical symptoms and reveals that clinical trajectories are neither linear nor synchronous.

In the frame of this model, the questions on the role of gender and age at onset obtain new meaning, and should be viewed from a much different and novel perspective.

Aim of the study

The aim of the current study was to explore the possible role of gender, age at onset of psychotic symptoms, and duration as predictors of the long-term course, and subsequently of outcome in patients with schizophrenia, on the basis of cross-sectional data. The analysis was done in the frame of the newly proposed model of staging for schizophrenia.

Materials and Methods

Study sample

The study sample included patients with a DSM-IV or DSM-5 diagnosis of schizophrenia.

Eligible patients were stabilized patients, and all were treated with medication based on therapists' judgment. They were either inpatients prior to discharge or outpatients, and were collected in a number of clinical settings, including academic units, clinics, and hospitals across different countries. There were no interventions associated with the current study. Patients were excluded if they had a coexisting diagnosis of substance abuse or dependence or a concurrent medical or neurological disorder according to their medical records. There was much effort to exclude organic mental disorders and more specifically dementia of any kind, according to the clinical judgment of the investigators.

All clinical evaluations were performed by trained psychiatrists. The study obtained approval by the Research Ethical Committee of the Aristotle University Medical School, Thessaloniki, Greece, and the other participating centers. Informed consent was obtained from all patients after a detailed description of the study procedures. Twenty-nine centers from 25 countries around the world participated in the study and contributed a total of 2358 patients (Table 1).

The same study sample had been used in a previous study of the same research group in order to develop a staging model of schizophrenia. Details on the method of diagnosis, variability among centers, and related issues are discussed in that paper.[1]

Measurements

The study collected sociodemographic information on patients with schizophrenia (age and gender) together with a cross-sectional assessment using the PANSS.[3-7] The PANSS is a 30-item rating scale developed by Kay and colleagues[4] to assess dimensions of schizophrenia symptoms and their severity. Items were initially compacted to resolve three scales: Positive (7 items), Negative (7 items), and GP (16 items). In this study, we used the modified version which includes four dimensions: Positive, Negative, GP, and Excited symptoms,[7] and we also computed the scores of Po, Ne, EH, DA, and Ncog proposed by our previously published analysis.[1] Trained interviewers administered the PANSS during structured clinical interviews and scored items on a scale from 1 (asymptomatic) to 7 (extremely symptomatic).

Data pertaining to the total duration of the illness (not duration of untreated psychosis) as well as age at onset were also collected.

Grouping of patients

Patients were grouped according to gender (males vs females) and also according to duration in seven groups (<5, 5-10, 11-15, 16-20, 21-25, 26-30, and >31) and according to age at onset in four groups: very early onset (at age <15), early onset (at age 15-24), late onset (at age 25-34), and very late onset (at age >34).

Concept of the method

First of all, it is important to note again that the data of the current study were cross-sectional, and therefore age, duration of illness, and stages were used in order to create a proxy for the long-term follow-up which was not available.

The method of the current study is novel, since it is based on a recently developed staging model of schizophrenia (Figure 1), which is identical for both genders.[1] This model constitutes a radical change in our understanding of the progress of schizophrenia and proposes stages as the best index of progression rather than duration or age. However, this method, by putting the problem on this new basis, also points to the fact that there is a cyclical correlation concerning many variables, especially between current age, age at onset, and duration. Patients with earlier age at onset tend to be younger, because they enter the health system at a younger age, and they tend to have longer duration of illness after controlling for age. Very late onset patients would be expected to suffer from a more severe neurocognitive disorder because of their advanced age. Therefore, the identification of the pure effect of the above variables on the long-term progression and outcome of the disorder is a difficult problem to analyze adequately.

For the current analysis, the effect on the long-term course and outcome was estimated on the basis of the following variables:

- Current mean age of subgroups within a specific stage of the disease could be used as a proxy for the age of transition between stages.
- The comparison of mean scores for Po, Ne, DA, EH, and Ncog of subgroups within a specific stage could give information concerning the effect on the severity of symptomatology or its pattern after controlling for the stage of progress.

It would be important to utilize age as a covariate when necessary.

For comparison reasons, a naïve method was also utilized and included the calculation of Pearson correlation coefficients between age, age at onset, and duration and the classical PANSS scales P, N, and GP.

Data analyses

The statistical analysis included the creation of tables with descriptive statistics.

Differences between groups were tested with the analysis of variance (ANOVA) or with analysis of covariance (ANCOVA) depending on the set of variables and the presence of confounders. The Scheffe test was used as the post hoc test.

Pearson correlation coefficients were also calculated to investigate the relationship between variables.

https://doi.org/10.1017/S1092852921000742 Published online by Cambridge University Press

Table 1. Composition of the Study Sample in Terms of Country of Origin, Sex, Age, Age at Onset, and Duration of Illness

			M		F	Age		Age at Onset		Duration	
Country	n	%	n	%	n	Mean	SD	Mean	SD	Mean	SD
Belgium	365	15.48	246	67.40	119	39.13	9.45	24.11	5.91	15.02	8.73
Bulgaria	31	1.31	17	54.84	14	44.94	12.18	23.61	4.50	21.32	10.99
Canada	30	1.27	15	50.00	15	56.67	12.77	24.70	6.51	31.97	11.98
Czech Rep	556	23.58	302	54.32	254	30.80	8.12	29.34	7.76	1.46	1.90
Finland	10	0.42	4	40.00	6	38.10	9.04	28.60	6.88	9.50	8.77
France	69	2.93	47	68.12	22	46.77	12.03	25.14	7.44	21.62	11.72
Germany	56	2.37	40	71.43	16	37.36	12.15	25.23	6.11	12.13	11.28
Greece	184	7.80	112	60.87	72	33.61	10.67	23.67	6.34	9.95	8.89
Hungary	108	4.58	51	47.22	57	41.04	13.25	27.49	10.29	13.55	10.85
India	47	1.99	30	63.83	17	34.13	9.77	25.07	6.67	9.05	7.18
Ireland	98	4.16	80	81.63	18	31.55	12.88	28.43	12.43	3.12	3.95
Italy	50	2.12	33	66.00	17	35.46	11.94	23.44	6.02	12.02	10.19
Latvia	74	3.14	30	40.54	44	44.51	12.77	26.59	10.36	17.92	12.55
Lithuania	50	2.12	27	54.00	23	37.74	13.39	23.06	7.26	14.68	11.43
Montenegro	50	2.12	24	48.00	26	40.46	11.58	21.78	4.37	18.68	10.85
Nigeria	93	3.94	43	46.24	50	37.83	10.14	27.82	8.61	10.01	7.96
Poland	55	2.33	28	50.91	27	36.55	10.96	25.22	7.76	11.33	9.30
Portugal	18	0.76	7	38.89	11	37.72	9.58	24.72	10.45	13.00	11.15
Romania	37	1.57	18	48.65	19	46.46	9.84	28.11	7.46	18.35	10.61
Russia	50	2.12	47	94.00	3	41.14	10.22	23.42	5.79	17.72	10.57
Serbia	50	2.12	45	90.00	5	39.46	11.66	22.66	5.27	16.80	11.12
South Africa	71	3.01	58	81.69	13	31.08	8.77	23.17	6.91	7.92	7.31
Spain	60	2.54	40	66.67	20	39.77	8.70	26.75	8.22	13.02	9.42
Sweden	39	1.65	21	53.85	18	55.26	11.83	26.15	10.19	29.10	11.84
Turkey	107	4.54	64	59.81	43	42.61	11.51	27.64	9.07	14.97	8.98
Total	2358	100.00	1429	60.60	929	37.22	11.87	26.16	8.07	11.06	10.94

Abbreviations: %, percentage; F, females; M, males; n, number of subjects; SD, standard deviation.

Results

Sociodemographic characteristics

The study population consisted of 2358 patients; 929 females (39.40%) and 1429 males (60.60%), aged 37.21 ± 11.87 years old (range 16-81 years) with the DSM-IV or DSM-5 diagnosis of schizophrenia.[8,9] Their age at onset was 26.16 ± 8.07 years, and their illness duration was 11.05 ± 10.93 years (range 0-54; Table 1).

In our study sample, only a negligible minority (eight patients; 0.3%) had age at onset >55 years of age. Thus, the effect of organic (mostly vascular pathology) on the etiopathogenesis of the disorder is considered to be negligible. However, an effect on current symptoms could not be ruled out.

Effect of gender

ANCOVA with gender as the categorical variable, duration, age at onset, Po, Ne, DA, EH, and Ncog as dependent variables, and age as covariate at each stage separately returned the following:

- Stage 1: Wilks: 0.965, $F = 3$, effect df: 6, error df: 502, $P = .006$. The Scheffe post hoc test returned significant results for age at onset (males 25.26 ± 7.65 vs females 27.91 ± 9.08; $P < .001$), Po (males 1.28 ± 0.81 vs females 1.13 ± 0.80; $P = -.036$), and DA (males −0.42 ± 0.75 vs females −0.25 ± 0.80; $P = .014$).
- Stage 2: Wilks: 0.975, $F = 3$, effect df: 6, error df: 635, $P = .013$. The Scheffe post hoc test returned significant results for age at onset (males 25.71 ± 7.81 vs females 28.18 ± 9.16; $P < .001$).
- Stage 3: Wilks: 0.951, $F = 3$, effect df: 6, error df: 605, $P < .001$. The Scheffe post hoc test returned significant results for age at onset (males 25.23 ± 6.46 vs females 27.61 ± 8.23; $P < .001$) and Ne (males 0.12 ± 0.86 vs females −0.16 ± 0.89; $P < .001$).
- Stage 4: Wilks: 0.943, $F = 3$, effect df: 6, error df: 584, $P < .001$. The Scheffe post hoc test returned significant results for age at onset (males 24.15 ± 7.02 vs females 27.52 ± 9.35; $P < .001$), Ne (males 0.21 ± 1.00 vs females −0.08 ± 0.96; $P < .001$), and DA (males −0.48 ± 0.69 vs females −0.33 ± 0.75; $P = .011$).

https://doi.org/10.1017/S1092852921000742 Published online by Cambridge University Press

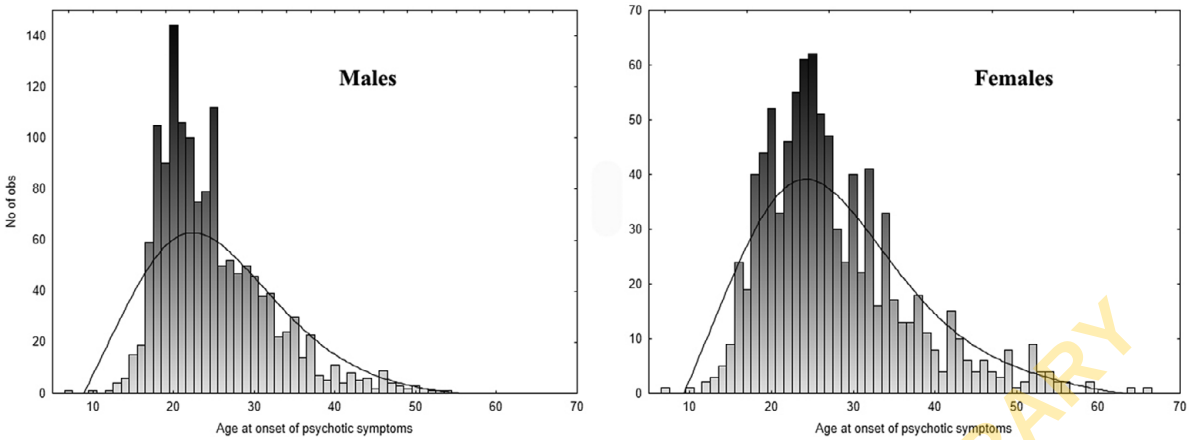

Figure 2. Distribution of the age at onset separately for genders.

Effect of age at onset

The age at onset manifested a distribution with a single peak, skewed toward younger ages for both genders (Figure 2). The mean was 25.08 ± 7.27, the median was 23, and the mode was 20 years for males, and the respected ages were 27.81 ± 8.92, 26, and 25 for females.

The ANOVA results with stage and onset group as grouping variables, and duration, Po, Ne, DA, EH, and Ncog as dependent variables suggested a significant effect for stage (Wilks: 0.668, $F = 56.41$, Effect df: 18, Error df: 6611, $P < .0001$), onset group (Wilks: 0.949, $F = 6.84$, Effect df: 18, Error df: 6611, $P < .0001$), as well as their interaction (Wilks: 0.962, $F = 1.69$, Effect df: 54, Error df: 119E2, $P = .001$).

Of interest would be the results on the interaction of onset group with stage and specifically only those differences within the same stage. The Scheffe post hoc test concerning duration returned significant results of interest concerning only stage 4 and very late onset (7.53 ± 1.22 years) vs very early (27.22 ± 3.52 years; $P = .02$) and early onset (14.782 ± 0.59 years; $P = .02$). There were no significant findings of interest concerning Po, Ne, EH, DA or Ncog.

In order to test whether the differences in duration of illness were in fact a confounding effect of age, ANCOVA was performed with the patients belonging to stage 4 alone, with onset group as categorical variable, duration as dependent and age as covariate. This confirmed there is a true difference in duration (df: 3, $F = 834$, $P < .001$) independent of age.

Effect of duration of illness

The duration also manifested a distribution with a single peak, skewed toward younger ages for both genders. The mean was 11.03 ± 10.66, the median was 8, and the mode was 0 years for males, and the respected values were 11.09 ± 11.36, 7, and 0 for females.

The ANOVA results with stage and duration group as grouping variables, and age at onset, Po, Ne, DA, EH, and Ncog as dependent variables suggested a significant effect for stage (Wilks: 0.228, $F = 250.7$, Effect df: 18, Error df: 6577, $P < .0001$), duration group (Wilks: 0.901, $F = 6.9$, Effect df: 36, Error df: 102E2, $P < .0001$) as well as their interaction (Wilks: 0.940, $F = 1.3$, Effect df: 108, Error df: 133E2, $P = .009$).

Of interest would be the results on the interaction of duration group with stage and specifically only those differences within the same stage. The Scheffe post hoc test concerning age at onset, Po, Ne, DA, EH, and Ncog did not return any significant results.

Analysis without taking stages into consideration and with classical PANSS subscales (naïve analysis)

Age correlated significantly but weakly with N ($R = 0.09$) and GP ($R = 0.09$). Age at onset correlated also weakly with P ($R = -0.06$), N ($R = -0.10$), and GP ($R = -0.05$). Weak were also the correlations of duration with P ($R = 0.06$), N ($R = 0.18$), and GP ($R = 0.14$). All the above coefficients were significant at $P < .01$.

The ANCOVA with the use of the whole study sample and with gender as grouping variable, age at onset, duration, P, N, and GP as dependent variables, and age as covariate suggested a significant effect of gender (Wilks: 0.968, $F = 20$, Effect df: 2, Error df: 2352, $P < .0001$). The Scheffe post hoc test revealed significant differences concerning age at onset (males 25.08 ± 0.19 vs females 27.81 ± 0.23; $P < .001$) and N (males 18.77 ± 0.19 vs females 17.11 ± 0.24; $P < .001$).

Discussion

In spite of the extended literature and the existence of much data, our understanding of the mechanisms underlying schizophrenia is poor, and limited to the early phases of schizophrenia. On the other hand, the developmental trajectory of schizophrenia is thought to be driven by a complex process and the interaction of many factors including genetics with multiple risk and vulnerability thresholds that operate at serial yet crucial neurodevelopmental periods that cumulatively lead to the expression of disorder.[10]

The effect of gender

The results concerning gender suggest females have later age at onset (3 years of difference according to median and 5 years according to mode), but the same duration of illness with males at each stage. Therefore, the difference in age at onset does not seem to have any effect on the rate of progress of the illness, when progress is considered in the frame of the model, recently proposed by our group.[1] On the other hand, females manifest fewer positive symptoms (lower Po) at the first stage, fewer negative symptoms

https://doi.org/10.1017/S1092852921000742 Published online by Cambridge University Press

(lower Ne) at later stages, and more depression and anxiety (higher DA) during almost all later stages. These are maybe suggestive of a slightly better overall long-term outcome, but this difference is quantitative (difference in scores) rather than qualitative (no differences in the general model of progression), and interpretations of this observation are problematic.

The literature supports such a gender effect[11-17] which was observed already since the beginning of the 20th century on the age at onset.[18] There are some data suggesting that age at menarche could be negatively associated with age at onset,[19] and more specifically, a specific protective effect of estrogens through down regulation of D2 receptors could be in place.[20-23] In support to this theory, there are some data on the beneficial effect of adjunctive estrogen therapy in refractory female cases.[24-28]

Explanations based on social factors[29] or biases in the diagnosis and identification of schizophrenia have been proposed, but all were rejected.[30,31] The magnitude of the difference between sexes is reported to vary depending on the definition of the age at onset and the method of assessing it, but it is probably 3 to 3.5 years,[13,20,31,32] and this is in accord with our findings. However, a meta-analysis of 46 selected epidemiological studies reported that this difference is only one year in magnitude,[33] but there seems to be important flaws in the data from several countries.[34,35] There are also some data suggesting a higher lifetime risk for males to develop schizophrenia[36-40] in combination with a worse outcome.[41,42]

On the other hand, some authors suggest the presence of a bimodal distribution in the age at onset in females with a second peak at menopausal age,[11,30] but our data do not support this.

The effect of age at onset

The results concerning age at onset suggest that in contrast to what is believed, for both sexes, there is a single peak in the distribution of age at onset. In addition, surprisingly, early onset patients manifested slower progress of the illness, especially during the later stages, and this is independent of the neurocognitive decline which might be expected to occur earlier in the course of the illness (with shorter duration) in very late onset patients. No quantitative differences in symptom scores were detected in relationship to the age at onset.

These results are in contrast with the reports on the presence of a bimodal distribution in the age at onset in females with a second peak around the menopausal age.[11,30] In our study sample, only a negligible minority (eight patients; 0.3%) had age at onset >55 years of age. This is a strength of this study, as very late onset may be driven by different, often organic causes.

They are also in contrast with reports which detected a small but clearly adverse correlation between age at onset and a number of course and outcome indicators including hospitalizations, more negative symptoms, poorer social/occupational functioning, and poorer global outcome.[43] Overall, the literature is in contrast to our findings, and it suggests that the course and outcome of early onset patients is slightly worse. However, methodological problems and especially sample attrition, with those patients with poor outcome being more likely to stay during follow-up, might determine the results.[44] As a consequence of these factors, the onset of schizophrenia in childhood—very rare—and in youth seems to be associated with particularly severe socioeconomic consequences in the further course of the disorder.[45-48]

On the other hand, in support of our findings are the results of a longitudinal study which reported the presence of a very high variability, indicative of no clear effect of age at onset.[49]

The effect of duration of being ill

While the general model, as described elsewhere,[1] was based on duration as the best proxy for progress, apart from the identification of stages, there was no other effect of duration. This refers to total duration of illness, not duration of untreated psychosis.

There are a lot of data in the literature which support the fluctuation of symptoms with duration of the illness and are essentially in accord with our model,[50] but overall the data do not support a relationship of age (which is a proxy for duration) and symptomatology.[51]

Overall, our data are in accord with the literature and suggest there is no interaction of gender, age at onset, and duration of illness to influence the long-term course of schizophrenia.

Naïve analysis

When a naïve analysis was performed, age correlated significantly but weakly with N and GP, age at onset also weakly with P, N, and GP, and duration with P, N, and GP. Females had delayed age at onset and fewer negative symptoms. The results of the naïve analysis, though generally in accord with the more sophisticated previous analysis, fail to elucidate the whole picture and at many points give a misleading impression (eg, positive symptoms increase with age and prolonged duration or females have a better overall outcome because of delayed onset).

These results are in accord with the literature as it is already analyzed above.

Strengths and limitations of the current study

The strengths of the current study include the large study sample which is one of the largest so far in the literature investigating the underlying mental functioning in patients with schizophrenia and the first in combination with a staging method. An additional strength is the multicenter and multinational characteristic of the sample.

The most important limitation of the study is that it utilized a cross-sectional design with the utilization of limited demographic and clinical information or treatment resistance status of the patients and these were combined with lack of long-term follow-up of patients.

A further limitation is that the study sample was not epidemiologically selected and therefore may not represent the general population of patients with schizophrenia. Instead, it represents those patients with at least less than ideal remission who remained in contact with mental health services for several years. It is unclear whether the differences observed among countries were because of this selection method; however, such a nonsystematic heterogeneity among countries is expected and does not seem to determine the overall outcome and results of the study.

Conclusion

If it is true that schizophrenia can manifest at different ages and with different symptoms, we should make sure that, in all these cases, we are really dealing with the same disorder, which was the case of our two previous papers.[1] With this model as a starting point, we analyzed the effect of gender, age at onset, and duration of illness, as well as their interaction.

Our results confirmed a later onset and a possibly more benign course and outcome in females. Age at onset manifested a single peak in both genders, and surprisingly, earlier onset was related to a slower progression of the illness. No effect of duration has been detected.

https://doi.org/10.1017/S1092852921000742 Published online by Cambridge University Press

These results are partially in accord with the literature, but some deviate sharply, as a consequence of the different starting point of our methodology (a novel staging model), which in our opinion corrected for confounding effects. Future research should focus on the therapeutic policy and implications of these results in more representative samples.

Data Availability Statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions. Conception and design of the study: K.N.F.; Acquisition of data: all authors; Analysis of data: K.N.F.; Drafting the manuscript or figures: K.N.F.; Reviewing subsequent versions of manuscript: all authors.

Disclosures. None pertaining to the current study. Several of the authors have received grants and support from the pharmaceutical industry, but this had no influence on the results and interpretation and the writing of the current study.

Funding Statement. M.B. is supported by an NHMRC Senior Principal Research Fellowship (APP1059660 and APP1156072).

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