Gender, age at onset and duration of being ill as predictors for the long-term course and outcome of Schizophrenia: An international multi-center study

Running head: Effect of gender, age at onset and duration in schizophrenia

Authors: Konstantinos N Fountoulakis¹, Elena Dragioti^{2,3}, Antonis T Theofilidis¹, Tobias Wiklund^{2,3}, Xenofon Atmatzidis^{2,3}, Ioannis Nimatoudis¹, Erik Thys⁴, Martien Wampers^{4,5}, Luchezar Hranov⁶, Trayana Hristova⁶, Daniil Aptalidis⁶, Roumen Milev⁷, Felicia Iftene⁷, Filip Spaniel⁸, Pavel Knytl⁸, Petra Furstova⁸, Tiina From⁹, Henry Karlsson⁹, Maija Walta⁹, Raimo K R Salokangas⁹, Jean-Michel Azorin^{10,11}, Justine Bouniard^{10,11}, Julie Montant^{10,11}, Georg Juckel¹², Ida S Haussleiter¹², Athanasios Douzenis¹³, Ioannis Michopoulos¹³, Panagiotis Ferentinos¹³, Nikolaos Smyrnis¹⁴, Leonidas Mantonakis¹⁴, Zsófia Nemes¹⁵, Xenia Gonda¹⁶, Dora Vajda¹⁶, Anita Juhasz¹⁶, Amresh Shrivastava¹⁷, John Waddington¹⁸, Maurizio Pompili¹⁹, Anna Comparelli¹⁹, Valentina Corigliano¹⁹, Elmars Rancans²⁰, Alvydas Navickas^{21,22,23}, Jan Hilbig^{21,22,23}, Laurynas Bukelskis^{21,22,23}, Lidija I Stevovic^{24,25,26}, Sanja Vodopic^{24,25,26}, Oluyomi Esan²⁷, Oluremi Oladele²⁷, Christopher Osunbote²⁷, Janusz K Rybakowski²⁸, Pawel Wojciak²⁸, Klaudia Domowicz²⁸, Maria L Figueira²⁹, Ludgero Linhares²⁹, Joana Crawford²⁹, Anca-Livia Panfil³⁰, Daria Smirnova³¹, Olga Izmailova³¹, Dusica Lecic-Tosevski^{32,33}, Henk Temmingh³⁴, Fleur Howells³⁴, Julio Bobes³⁵, Maria P Garcia-Portilla³⁵, Leticia García-Alvarez³⁵, Gamze Erzin³⁶, Hasan Karadağ³⁶, Avinash De Sousa³⁷, Anuja Bendre³⁷, Cyril Hoschl⁸, Cristina Bredicean³⁸, Ion Papava³⁸, Olivera Vukovic³⁹, Bojana Pejuskovic⁴⁰, Vincent Russell⁴⁰, Loukas Athanasiadis⁴¹, Anastasia Konsta⁴¹, Dan Stein⁴², Michael Berk^{43,44,45,46}, Olivia Dean^{43,44,45,46}, Rajiv Tandon⁴⁷, Siegfried Kasper⁴⁸, Marc De Hert^{4,5,49}

Affiliations

¹3rd Department of Psychiatry, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece.

²Department of Medical and Health Sciences (IMH), Faculty of Health Sciences, Linköping University, Linköping, Sweden.

³Hallunda Psychiatric Outpatient Clinic, Stockholm Psychiatric Southwest Clinic, Karolinska Huddinge University Hospital, Huddinge, Sweden.

⁴University Psychiatric Center, Katholieke Universiteit Leuven, Kortenberg, Belgium.

⁵Department of Neurosciences, Katholieke Universiteit Leuven, Leuven, Belgium.

⁶University Multiprofile Hospital for Active Treatment in Neurology and Psychiatry "Sveti Naum", Sofia, Bulgaria.

⁷Department of Psychiatry, Queen's University, Providence Care Hospital, Kingston, Ontario, Canada.

⁸National Institute of Mental Health, Klecany, Czech Republic.

⁹Department of Psychiatry, University of Turku, Turku, Finland.

¹⁰Department of Psychiatry, Sainte Marguerite University Hospital, Marseille, France.

¹¹Timone Institute of Neuroscience, Marseille, France.

¹²Department of Psychiatry, Ruhr University Bochum, Bochum, Germany.

DOI: 10.1017/S1092852921000742

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article may be cited using its DOI.

- 54 ¹³2nd Department of Psychiatry, National and Kapodistrian University of Athens,
55 Athens, Greece.
- 56 ¹⁴Department of Psychiatry, National and Kapodistrian University of Athens School
57 of Medicine, Eginition Hospital, Athens, Greece.
- 58 ¹⁵Nyíró Gyula Hospital, Budapest, Hungary.
- 59 ¹⁶Department of Psychiatry and Psychotherapy, Semmelweis University,
60 Budapest, Hungary.
- 61 ¹⁷Western University, London, Ontario, Canada.
- 62 ¹⁸Department of Molecular and Cellular Therapeutics, Royal College of Surgeons
63 in Ireland, Dublin, Ireland.
- 64 ¹⁹Department of Neurosciences, Mental Health and Sensory Organs, Suicide
65 Prevention Center, Sant'Andrea Hospital, Sapienza University of Rome, Rome,
66 Italy.
- 67 ²⁰Department of Psychiatry and Narcology, Riga Stradins University, Riga, Latvia.
- 68 ²¹Department of Clinic of Psychiatric, Faculty of Medicine, Vilnius University,
69 Vilnius, Lithuania.
- 70 ²²Department of Psychosocial Rehabilitation, Vilnius Mental Health Center, Vilnius,
71 Lithuania.
- 72 ²³Department for Psychosis Treatment, Vilnius Mental Health Center, Vilnius,
73 Lithuania.
- 74 ²⁴Clinical Department of Psychiatry, Clinical Centre of Montenegro, Podgorica,
75 Montenegro.
- 76 ²⁵Department of Psychiatry, School of Medicine, University of Montenegro,
77 Podgorica, Montenegro.
- 78 ²⁶Clinical Department of Neurology, Clinical Centre of Montenegro, Podgorica,
79 Montenegro.
- 80 ²⁷Department of Psychiatry, College of Medicine, University of Ibadan, Ibadan,
81 Nigeria.
- 82 ²⁸Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan,
83 Poland.
- 84 ²⁹Department of Psychiatry and Mental Health, Santa Maria University Hospital,
85 Lisbon, Portugal.
- 86 ³⁰University of Medicine and Pharmacy of Târgu Mures, Târgu Mures, Romania.
- 87 ³¹Department of Psychiatry, Samara Psychiatric Hospital, Inpatient Unit, Samara
88 State Medical University, Samara, Russia.
- 89 ³²Institute of Mental Health, Belgrade, Serbia.
- 90 ³³Serbian Academy of Sciences and Arts, Belgrade, Serbia.
- 91 ³⁴Department of Psychiatry and Mental Health, University of Cape Town, Cape
92 Town, South Africa.
- 93 ³⁵Department of Psychiatry, University of Oviedo and Centro de Investigación
94 Biomédica en Red de Salud Mental (CIBERSAM), Oviedo, Spain.
- 95 ³⁶Psychiatry Department, Diskapi Yildirim Beyazit Training and Research Hospital,
96 Ankara, Turkey.
- 97 ³⁷Department of Psychiatry, Lokmanya Tilak Municipal Medical College, Mumbai,
98 India.
- 99 ³⁸University of Medicine and Pharmacy of Timisoara, Timisoara, Romania.
- 100 ³⁹Institute of Mental Health, School of Medicine, University of Belgrade, Belgrade,
101 Serbia.
- 102 ⁴⁰Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont
103 Hospital, Dublin, Ireland.
- 104 ⁴¹1st Department of Psychiatry, Faculty of Medicine, School of Health Sciences,
105 Aristotle University of Thessaloniki, Thessaloniki, Greece.
- 106 ⁴²MRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry
107 and Mental Health, University of Cape Town, Cape Town, South Africa.
- 108 ⁴³IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Deakin
109 University, Geelong, Australia.

Accepted Manuscript: Authors' Copy

⁴⁴Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Victoria, Australia.

⁴⁵Centre for Youth Mental Health, The Florey Institute for Neuroscience and Mental Health, Parkville, Victoria, Australia.

⁴⁶Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia.

⁴⁷Department of Psychiatry, University of Florida, Gainesville, Florida, USA.

⁴⁸Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria.

⁴⁹Antwerp Health Law and Ethics Chair-AHLEC University, Antwerpen, Belgium.

For the field: Psychotherapy and psychopathology

Corresponding author: Konstantinos N. Fountoulakis, 6, Odysseos str (1st Parodos Ampelonon str.), 55535 Pylaia, Thessaloniki, Greece; E-mail: kfount@med.auth.gr

Submitted 18 March 2021

Accepted 07 July 2021

Abstract

Introduction:

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.

Materials and 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; PANSS as well as relevant clinicodemographic data were gathered. ANOVA and ANCOVA 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 ($p < 0.001$) and lower rates of negative symptoms ($p < 0.01$) and higher depression/anxiety measures ($p < 0.05$) 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 ($p = 0.001$). 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.

Key words: Gender; age at onset; duration; predictors; long term course; outcome; Schizophrenia

162

163 **Significant outcomes**

164

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

169

170 **Limitations of the current study**

171

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

179

180 **Data availability statement**

181 The data that support the findings of this study are available from the

182 corresponding author upon reasonable request.

183

1. 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 PANSS factors in their item composition. Therefore and in order to avoid confusion, the new factors were named Po (instead of P), Ne (instead of N), EH (for excitation/hostility), DA (reflecting aspects of general psychopathology 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

Accepted Manuscript: Authors' Copy

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.

2. Materials and methods

2.1 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.

2.2 Measurements

The study collected socio-demographic information on patients with schizophrenia (age and gender) together with a cross-sectional assessment using the Positive and Negative Syndrome Scale (PANSS)³⁻⁷. The PANSS is a 30-item rating scale developed by Kay and colleagues⁴ to assess dimensions of schizophrenia symptoms and their severity. Items were initially compacted to resolve three scales: Positive (7 items), Negative (7 items), and General Psychopathology (GP) (16 items). In this study we used the modified version which includes four dimensions: Positive, Negative, GP and Excited symptoms⁷ and we also computed the scores of Po, Ne, EH, DA and Ncog proposed by our previously published analysis¹. 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.

2.3 Grouping of patients

Patients were grouped according to gender (males vs. females) and also according to duration in 7 groups (<5, 5-10, 11-15, 16-20, 21-25, 26-30, and >31) and according to age at onset in 4 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).

2.3 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 genders¹. 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, it 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

2.4 Data analyses

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

Accepted Manuscript: Authors' Copy

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.

3. Results

3.1 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 -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 (8 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.

3.2. 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, $p=0.006$. The Scheffe post hoc test returned significant results for age at onset (males 25.26 ± 7.65 vs. females 27.91 ± 9.08 ; $p<0.001$), Po (males 1.28 ± 0.81 vs. females 1.13 ± 0.80 ; $p=0.036$) and DA (males -0.42 ± 0.75 vs. females -0.25 ± 0.80 ; $p=0.014$)
- Stage 2: Wilks: 0.975, $F=3$, effect df: 6, error df: 635, $p=0.013$. The Scheffe post hoc test returned significant results for age at onset (males 25.71 ± 7.81 vs. females 28.18 ± 9.16 ; $p<0.001$).
- Stage 3: Wilks: 0.951, $F=3$, effect df: 6, error df: 605, $p<0.001$. The Scheffe post hoc test returned significant results for age at onset (males 25.23 ± 6.46 vs.

341 females 27.61 ± 8.23 ; $p < 0.001$) and Ne (males 0.12 ± 0.86 vs. females -
342 0.16 ± 0.89 ; $p < 0.001$).

343• Stage 4: Wilks: 0.943, $F=3$, effect df: 6, error df: 584, $p < 0.001$. The Scheffe
344 post hoc test returned significant results for age at onset (males 24.15 ± 7.02 vs.
345 females 27.52 ± 9.35 ; $p < 0.001$), Ne (males 0.21 ± 1.00 vs. females -0.08 ± 0.96 ;
346 $p < 0.001$) and DA (males -0.48 ± 0.69 vs. females -0.33 ± 0.75 ; $p = 0.011$).

348 **3.3 Effect of age at onset**

350 The age at onset manifested a distribution with a single peak, skewed towards
351 younger ages for both genders (figure 2). The mean was 25.08 ± 7.27 , the median
352 was 23 and the mode was 20 years for males and the respected ages were
353 27.81 ± 8.92 , 26 and 25 for females

354 The ANOVA results with stage and onset group as grouping variables and
355 duration, Po, Ne, DA, EH and Ncog as dependent variables suggested a significant
356 effect for stage (Wilks: 0.668, $F=56.41$, Effect df: 18, Error df: 6611, $p < 0.0001$),
357 onset group (Wilks: 0.949, $F=6.84$, Effect df: 18, Error df: 6611, $p < 0.0001$) as
358 well as their interaction (Wilks: 0.962, $F=1.69$, Effect df: 54, Error df: 119E2,
359 $p = 0.001$).

360 Of interest would be the results on the interaction of onset group with stage and
361 specifically only those differences within the same stage. The Scheffe post hoc
362 test concerning duration returned significant results of interest concerning only
363 stage 4 and very late onset (7.53 ± 1.22 years) vs. very early (27.22 ± 3.52 years;
364 $p = 0.02$) and early onset (14.782 ± 0.59 years; $p = 0.02$). There were no significant
365 findings of interest concerning Po, Ne, EH, DA or Ncog.

366 In order to test whether the differences in duration of illness were in fact a
367 confounding effect of age, ANCOVA was performed with the patients belonging to
368 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, $F=834$, $p<0.001$) independent of age.

3.4 Effect of Duration of illness

The duration also manifested a distribution with a single peak, skewed towards 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, $p<0.0001$), duration group (Wilks: 0.901, $F=6.9$, Effect df: 36, Error df: 102E2, $p<0.0001$) as well as their interaction (Wilks: 0.940, $F=1.3$, Effect df: 108, Error df: 133E2, $p=0.009$).

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 at did not returned any significant results.

3.5 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 $p<0.01$.

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, $p<0.0001$). The Scheffe post hoc test revealed significant differences concerning age at onset (males 25.08 ± 0.19 vs. females 27.81 ± 0.23 ; $p<0.001$) and N (males 18.77 ± 0.19 vs. females 17.11 ± 0.24 ; $p<0.001$).

4. 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.

4.1 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 (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 effect¹¹⁻¹⁷ which was observed already since the beginning of the 20th century on the age at onset¹⁸. There are some data suggesting that age at menarche could be negatively associated with age at onset¹⁹ and more specifically a specific protective effect of estrogens through down regulation of D2 receptors could be in place²⁰⁻²³. In support to this theory there are some data on the beneficial effect of adjunctive oestrogen therapy in refractory female cases²⁴⁻²⁸.

Explanations based on social factors²⁹ 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 3-3.5 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 magnitude³³ 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 schizophrenia³⁶⁻⁴⁰ 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.

4.2 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. Also 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 (8 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 outcome⁴³. 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 results⁴⁴. 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 disorder⁴⁵⁻⁴⁸.

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 onset⁴⁹.

4.3 The effect of duration of being ill

While the general model, as described elsewhere¹, 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 is 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 model⁵⁰ but overall the data do not support a relationship of age (which is a proxy for duration) and symptomatology⁵¹.

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.

4.4 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 (e.g. 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.

4.5 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 multi-center 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 info 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 non-systematic heterogeneity among countries is expected and does not seem to determine the overall outcome and results of the study.

4.6. 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.

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.

Accepted Manuscript: Authors' Copy

Disclosure information: 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

Author contribution:

conception and design of the study: KNF
acquisition of data: all authors
analysis of data: KNF
drafting the manuscript or figures: KNF
Reviewing subsequent versions of manuscript: all authors

Acknowledgments: MB is supported by a NHMRC Senior Principal Research Fellowship (APP1059660 and APP1156072).

Source of funding: There was no funding of any kind and from any source. All contributors worked without any financial gain.

References

1. Fountoulakis KN, Dragioti E, Theofilidis AT, et al. Staging of Schizophrenia With the Use of PANSS: An International Multi-Center Study. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. Nov 1 2019;22(11):681-697.
2. Fountoulakis KN, Dragioti E, Theofilidis AT, et al. Modeling psychological function in patients with schizophrenia with the PANSS: an international multi-center study. *CNS Spectr*. Apr 15 2020:1-9.
3. Kay SR. Positive-negative symptom assessment in schizophrenia: psychometric issues and scale comparison. *The Psychiatric quarterly*. Fall 1990;61(3):163-78.
4. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin*. 1987;13(2):261-76.
5. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry research*. Jan 1988;23(1):99-110.
6. Kay SR, Sandyk R. Experimental models of schizophrenia. *The International journal of neuroscience*. May 1991;58(1-2):69-82.
7. Kay SR, Sevy S. Pyramidal model of schizophrenia. *Schizophrenia bulletin*. 1990/01/01 1990;16(3):537-45. doi:10.1093/schbul/16.3.537
8. APA. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Association; 2013.
9. APA. *Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition Text Revision DSM-IV-TR*. American Psychiatric Association; 2000.
10. Davis J, Eyre H, Jacka FN, et al. A review of vulnerability and risks for schizophrenia: Beyond the two hit hypothesis. *Neurosci Biobehav Rev*. Jun 2016;65:185-94. doi:10.1016/j.neubiorev.2016.03.017
11. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. Jul 24 2014;511(7510):421-7. doi:10.1038/nature13595
12. Angermeyer MC, Kuhn L. Gender differences in age at onset of schizophrenia. An overview. *Eur Arch Psychiatry Neurol Sci*. Sep 1988;237(6):351-64.
13. Hambrecht M, Maurer K, Hafner H, Sartorius N. Transnational stability of gender differences in schizophrenia? An analysis based on the WHO study on determinants of outcome of severe mental disorders. *Eur Arch Psychiatry Clin Neurosci*. 1992/09 1992;242(1):6-12.
14. Hambrecht M, Maurer K, Hafner H. Gender differences in schizophrenia in three cultures. Results of the WHO collaborative study on psychiatric disability. *Soc Psychiatry Psychiatr Epidemiol*. May 1992;27(3):117-21. doi:10.1007/bf00788756
15. Messias EL, Chen CY, Eaton WW. Epidemiology of schizophrenia: review of findings and myths. *The Psychiatric clinics of North America*. Sep 2007;30(3):323-38. doi:10.1016/j.psc.2007.04.007
16. Morgan C, John S, Esan O, et al. The incidence of psychoses in diverse settings, INTREPID (2): a feasibility study in India, Nigeria, and Trinidad. *Psychol Med*. Jul 2016;46(9):1923-33. doi:10.1017/S0033291716000441
17. Ochoa S, Usall J, Cobo J, Labad X, Kulkarni J. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. *Schizophr Res Treatment*. 2012;2012:916198.
18. Kraepelin E. *Psychiatrie*, 8. Aufl. . Barth; 1909-1915.
19. Kilicaslan EE, Erol A, Zengin B, Cetinay Aydin P, Mete L. Association Between Age at Onset of Schizophrenia and Age at Menarche. *Noro Psikiyatr Ars*. Sep 2014;51(3):211-215. doi:10.4274/npa.y6675

- 615 20. Hafner H. From Onset and Prodromal Stage to a Life-Long Course of
616 Schizophrenia and Its Symptom Dimensions: How Sex, Age, and Other Risk
617 Factors Influence Incidence and Course of Illness. *Psychiatry J.*
618 2019;2019:9804836.
- 619 21. Gattaz WF, Behrens S, De Vry J, Hafner H. [Estradiol inhibits dopamine
620 mediated behavior in rats--an animal model of sex-specific differences in
621 schizophrenia]. *Fortschr Neurol Psychiatr.* Jan 1992;60(1):8-16. Oestradiol hemmt
622 Dopamin-vermittelte Verhaltensweisen bei Ratten--ein Tiermodell zur
623 Untersuchung der geschlechtsspezifischen Unterschiede bei der Schizophrenie.
- 624 22. Häfner H, Behrens S, De Vry J, Gattaz WF. Oestradiol enhances the
625 vulnerability threshold for schizophrenia in women by an early effect on
626 dopaminergic neurotransmission. *European Archives of Psychiatry and Clinical*
627 *Neuroscience.* 1991/07 1991;241(1):65-68.
- 628 23. Hafner H, Ehrenreich H, Gattaz W, Louza M, Riecher-Rossler A, Kulkarni J.
629 Oestrogen-A Protective Factor in Schizophrenia? *Current Psychiatry Reviews.*
630 2006/08/01 2006;2(3):339-352.
- 631 24. Akhondzadeh S, Nejatisafa AA, Amini H, et al. Adjunctive estrogen
632 treatment in women with chronic schizophrenia: a double-blind, randomized, and
633 placebo-controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry.* Sep
634 2003;27(6):1007-12.
- 635 25. Kulkarni J, Castella A, Downey M, et al. Results of two controlled studies
636 on estrogen: avenue to neuroprotection in schizophrenia. Risk and Protective
637 Factors in Schizophrenia: Steinkopff; 2002. p. 271-282.
- 638 26. Kulkarni J, de Castella A, Fitzgerald PB, et al. Estrogen in severe mental
639 illness: a potential new treatment approach. *Arch Gen Psychiatry.* Aug
640 2008;65(8):955-60.
- 641 27. Kulkarni J, Gavrilidis E, Hayes E, Heaton V, Worsley R. Special biological
642 issues in the management of women with schizophrenia. *Expert Rev Neurother.*
643 Jul 2012;12(7):823-33.
- 644 28. Kulkarni J, Gavrilidis E, Wang W, et al. Estradiol for treatment-resistant
645 schizophrenia: a large-scale randomized-controlled trial in women of child-
646 bearing age. *Mol Psychiatry.* Jun 2015;20(6):695-702.
- 647 29. Gureje O. Gender and schizophrenia: age at onset and sociodemographic
648 attributes. *Acta Psychiatr Scand.* May 1991;83(5):402-5.
- 649 30. Hafner H, Riecher-Rossler A, An Der Heiden W, Maurer K, Fatkenheuer B,
650 Löffler W. Generating and testing a causal explanation of the gender difference in
651 age at first onset of schizophrenia. *Psychol Med.* Nov 1993;23(4):925-40.
- 652 31. Hafner H, Riecher A, Maurer K, Löffler W, Munk-Jorgensen P, Stromgren E.
653 How does gender influence age at first hospitalization for schizophrenia? A
654 transnational case register study. *Psychol Med.* Nov 1989;19(4):903-18.
- 655 32. Hafner H, Hambrecht M, Löffler W, Munk-Jorgensen P, Riecher-Rossler A.
656 Is schizophrenia a disorder of all ages? A comparison of first episodes and early
657 course across the life-cycle. *Psychol Med.* Mar 1998;28(2):351-65.
- 658 33. Eranti SV, MacCabe JH, Bundy H, Murray RM. Gender difference in age at
659 onset of schizophrenia: a meta-analysis. *Psychol Med.* Jan 2013;43(1):155-67.
- 660 34. Murthy GV, Janakiramaiah N, Gangadhar BN, Subbakrishna DK. Sex
661 difference in age at onset of schizophrenia: discrepant findings from India. *Acta*
662 *Psychiatr Scand.* May 1998;97(5):321-5.
- 663 35. Gangadhar BN, Panner Selvan C, Subbakrishna DK, Janakiramaiah N. Age-
664 at-onset and schizophrenia: reversed gender effect. *Acta Psychiatr Scand.* Apr
665 2002;105(4):317-9. doi:10.1034/j.1600-0447.2002.1153.x
- 666 36. Iacono WG, Beiser M. Are males more likely than females to develop
667 schizophrenia? *Am J Psychiatry.* Aug 1992;149(8):1070-4.
- 668 37. Kirkbride JB, Fearon P, Morgan C, et al. Heterogeneity in incidence rates of
669 schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP
670 study. *Arch Gen Psychiatry.* Mar 2006;63(3):250-8.

38. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med.* Apr 28 2004;2(1):13.
39. Thorup A, Waltoft BL, Pedersen CB, Mortensen PB, Nordentoft M. Young males have a higher risk of developing schizophrenia: a Danish register study. *Psychol Med.* Apr 2007;37(4):479-84.
40. van der Werf M, Hanssen M, Kohler S, et al. Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia. *Psychol Med.* Jan 2014;44(1):9-16.
41. Goldstein JM, Tsuang MT, Faraone SV. Gender and schizophrenia: implications for understanding the heterogeneity of the illness. *Psychiatry research.* Jun 1989;28(3):243-53.
42. Gureje O, Bamidele RW. Gender and schizophrenia: association of age at onset with antecedent, clinical and outcome features. *Aust N Z J Psychiatry.* Jun 1998;32(3):415-23.
43. Immonen J, Jaaskelainen E, Korpela H, Miettunen J. Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis. *Early Interv Psychiatry.* Dec 2017;11(6):453-460.
44. Clemmensen L, Vernal DL, Steinhausen HC. A systematic review of the long-term outcome of early onset schizophrenia. *BMC psychiatry.* Sep 19 2012;12:150.
45. Asarnow JR. Children at risk for schizophrenia: converging lines of evidence. *Schizophrenia bulletin.* 1988/01/01 1988;14(4):613-31. doi:10.1093/schbul/14.4.613
46. Asarnow JR, Tompson MC, McGrath EP. Annotation: childhood-onset schizophrenia: clinical and treatment issues. *J Child Psychol Psychiatry.* Feb 2004;45(2):180-94.
47. Eggers C, Bunk D. The long-term course of childhood-onset schizophrenia: a 42-year followup. *Schizophrenia bulletin.* 1997;23(1):105-17.
48. Kendhari J, Shankar R, Young-Walker L. A Review of Childhood-Onset Schizophrenia. *Focus.* 2016/07 2016;14(3):328-332.
49. Hafner H, Maurer K, an der Heiden W. ABC Schizophrenia study: an overview of results since 1996. *Soc Psychiatry Psychiatr Epidemiol.* Jul 2013;48(7):1021-31.
50. van Os J, Howard R, Takei N, Murray R. Increasing age is a risk factor for psychosis in the elderly. *Social Psychiatry and Psychiatric Epidemiology.* 1995/07 1995;30(4):161-164.
51. Häfner H, Maurer K, Löffler W, et al. The ABC schizophrenia study: a preliminary overview of the results. *Social Psychiatry and Psychiatric Epidemiology.* 1998/07/13 1998;33(8):380-386.

713

714 **Figure 1:** Plot of factor scores (y-axis) vs. stages and sub-stages of illness
 715 progression

716 Po: Positive symptoms factor according to the model dimensions

717 Ne: Negative symptoms factor according to the model dimensions

718 EH: Excitement-hostility symptoms factor according to the model dimensions

719 DA: Depression and anxiety symptoms factor according to the model dimensions

720 Ncog: Neurocognitive deficit factor according to the model dimensions

721 The above factors come from an analysis previously published ¹ and they do not
 722 correspond to classic PANNS subscales

723

724

725

726

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

732
733

Country	N	%	M		F	Age		Age at onset		Duration	
			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

734
735

736 **Table 1:** Composition of the study sample in terms of country of origin, sex,
737 age, age at onset and duration of illness
738 M: males; F: females; N: number of subjects; % percentage SD: standard
739 deviation