Universität Basel
Fakultät für Psychologie

Sex and Gender Differences in Psychopathology and Neurocognition in Emerging Psychoses

Inaugural Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy to the Department of Psychology of the University of Basel by

Stephanie Menghini-Müller

from Lenzburg (AG), Switzerland

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Universität Basel

Fakultät für Psychologie

Approved by the Department of Psychology at the request of

Prof. Dr. Anita Riecher-Rössler

Prof. Dr. Roselind Lieb

Basel, _____

Prof. Dr. Jens Gaab

Universität Basel
Fakultät für Psychologie

Declaration of Authorship

I, Stephanie Menghini-Müller (born June 12, 1989), hereby declare that I have contributed independently and substantially to this dissertation without any assistance from third parties who are not indicated. I have used only the resources indicated and have cited all references. Published manuscripts or manuscripts submitted for publication were prepared in cooperation with coauthors and have not been submitted elsewhere for review or consideration, nor have they been published elsewhere. This dissertation includes the following three manuscripts:

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- Heitz, U., Studerus, E., Menghini-Müller, S., Papmeyer, M., Egloff, L., Ittig, S., Navarra, A., Andreou, C., Riecher-Rössler, A. (2017). Gender differences in first self-perceived signs and symptoms in patients with an at-risk mental state and first-episode psychosis. Early Intervention in Psychiatry, 13(3), 582-588.

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Abbreviations

APS	Attenuated Psychotic Symptoms
ARMS	At-Risk Mental State
ARMS-NT	At-Risk Mental State – Non Transitioned
ARMS-T	At-Risk Mental State – Transitioned
BIP	Basel Interview for Psychosis; Basler Interview zur Früherkennung von Psychosen
BLIPS	Brief Limited Intermitted Psychotic Symptoms
BPRS-E	Brief Psychiatric Rating Scale – Expanded
BSIP	Basel Screening Instrument for Psychosis
CAARMS	Comprehensive Assessment of At-Risk Mental State
DUI	Duration of Untreated Illness
DUP	Duration of Untreated Psychosis
EU-GEI	**EU**ropean network of national schizophrenia networks studying **G**ene-**E**nvironment **I**nteractions
FEP	First Episode Psychosis
FePsy	Basler Projekt zur **F**rüh**e**rkennung von **Psy**chosen
GAF	Global Assessment of Functioning
HC	Healthy Controls
WAIS-III	Wechsler Adult Intelligence Scale, 3rd ed.

Abstract

There has been large evidence that patients with psychotic disorders, such as schizophrenia, usually experience early signs of psychosis even before developing frank psychosis. In recent years, research into the field of early detection, in particular the identification of factors that increase disease risk, has received growing scientific and clinical interest. An intriguing research area in this field is the investigation of gender differences. The present dissertation aims to investigate (1) gender differences in symptomatology, drug use, comorbidity (i.e. substance use, affective and anxiety disorders) and global functioning in patients with an at-risk mental state (ARMS) for psychosis, (2) sex differences in cognitive functioning in ARMS patients and healthy controls (HC), (3) gender differences in the first self-perceived signs and symptoms in ARMS and first-episode psychosis (FEP) patients.

The first study demonstrated that gender differences in symptomatology and comorbidity in ARMS patients are similar to those seen in overt psychosis and in healthy controls. However, the observed differences were so small that they are probably not clinically meaningful. The second study showed that sex differences in cognitive functioning in ARMS are similar to those seen in healthy men and women. In particular, the female advantage in verbal learning and memory seems to be equally present in ARMS patients and HC. Our third study found only few and relatively small gender differences in the first self-perceived signs and symptoms. While men initially mainly noticed negative and cognitive symptoms, women first noticed (sub-threshold) positive and affective symptoms.

All in all, regarding emerging symptomatology and cognitive functioning, it seems that the above described differences between women and men – if present at all – are small and resemble those in the general population. Similarly, few gender differences were found regarding first self-perceived signs and symptoms.

Introduction

Early detection of psychosis

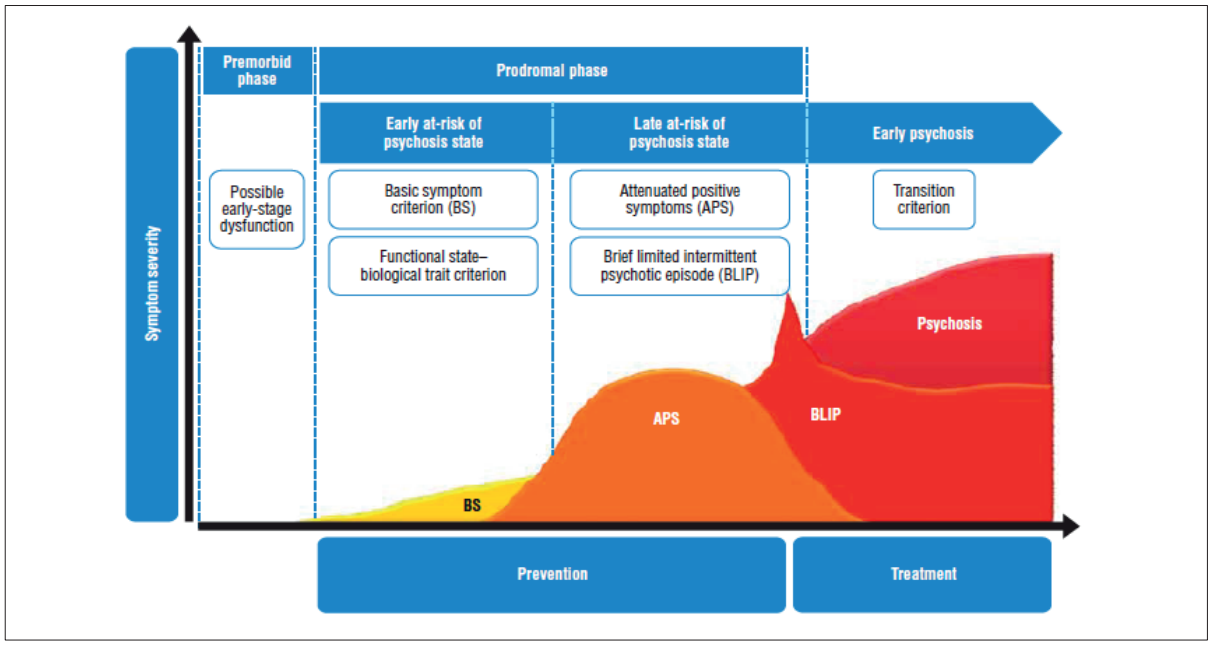
During the past two decades, there has been increasing interest in the early detection and intervention during the prodromal phase of a psychotic disorder. Patients often experience early signs of psychosis even 1 to 5 years prior to the first episode of frank illness (Riecher-Rössler et al., 2006). This delay in diagnosis and treatment has been described by two concepts, namely the duration of untreated psychosis (DUP) and the duration of untreated illness (DUI). Regarding DUP, patients suffer from productive psychotic symptoms, such as hallucinations or delusions, for an average of 1 to 3 years prior to the diagnosis of psychosis and its first treatment. DUI is a so-called 'unspecific prodromal phase' which lasts on average 2 to 5 years and already starts before DUP (Riecher-Rössler et al., 2006). The ABC study was one of the first studies that could show this delay on a methodologically sound basis (Häfner et al., 1998; Riecher et al., 1991). The results of this study suggest that the initial signs on average become apparent approximately 4.6 years before first admission and diagnosis of schizophrenia whereas the first psychotic symptoms occur on average 2.1 year prior to first admission (Häfner et al., 1993a). Another major finding of the ABC study was that most patients suffer from severe impairments and losses in numerous social domains such as independent living, partnership, education or work even before first admission (Häfner et al., 1995a). A longer DUP can have severe consequences. It has been demonstrated that the delay is associated with a worse long-term prognosis, worse overall functional outcome, lower levels of symptomatic and functional recovery, negative symptom severity (Murru et al., 2018; Perkins et al., 2005), poorer social functioning and treatment response (Perkins et al., 2005), stronger impairment of psychological and social development (Riecher-Rössler et al., 2006) and higher overall treatment costs (Lincoln et al., 1995; Ricciardi et al., 2008). Researchers and clinicians have therefore concentrated on the early detection and intervention of psychosis to improve the course of the disease. To prospectively identify people at-risk for psychosis and capture the

pre-psychotic phase, the construct of a clinical high-risk (CHR) state for psychosis has evolved (see Figure 1; Fusar-Poli et al., 2013). There have been two complementary sets of clinical features that have been used to diagnose the CHR state in individuals at-risk, namely ultra-high-risk (UHR) and basic symptoms (BS) criteria.

The UHR criteria comprise four main sets of clinical criteria: Attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), genetic risk and deterioration syndrome (GRD), and unspecified prodromal symptoms (UPS). They were defined to identify young people at high risk of developing a first episode of psychosis (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015). Different interview measures have been developed to assess UHR features and to determine whether individuals meet criteria for UHR (for a detailed description of the UHR criteria and their assessment, see Fusar-Poli et al., 2013). Meta-analytical findings confirm that the currently used interviews for psychosis prediction show an excellent overall prognostic performance, despite the significant differences in their criteria (Fusar-Poli et al., 2015). However, this excellent overall prognostic performance was mainly mediated by an outstanding ability of the instruments to rule out psychosis, at an expense of their ability to rule in psychosis (Fusar-Poli et al., 2015).

BS are subjectively experienced disturbances of different domains, including perception, thought processing, language and attention (Fusar-Poli et al., 2013; Schultze-Lutter, 2009). They were developed to identify the risk for psychosis even before functional impairment appeared (Schultze-Lutter et al., 2010). BS were originally assessed using the Bonn Scale for the Assessment of Basic Symptoms (BSABS, Klosterkötter et al., 1997). More recently, the Schizophrenia Proneness Instrument, Adult version (SPI-A, Schultze-Lutter et al., 2007), and the self-report Frankfurt Complaint Questionnaire (FCQ) have mainly been used (Uttinger et al., 2018).

Figure 1. Model of psychosis onset from the clinical high-risk state. The higher the line on the y-axis, the higher the symptom severity (Fusar-Poli et al., 2013)



BS: Basic Symptoms; APS: Attenuated Psychotic Symptoms; BLIP: Brief Limited Intermittent Psychotic episode.

Those who meet the at-risk criteria either by UHR or BS are termed "Clinical High-Risk" (CHR) or "At-Risk Mental State" (ARMS) patients. Patients who meet UHR criteria only are termed "Ultra-High-Risk" (UHR) patients (Fusar-Poli et al., 2012a). For this thesis, the term ARMS will be used to show that these individuals are already suffering from some symptoms and problems. It has been shown that less than 40% of patients identified as being in an ARMS will actually develop a psychotic disorder (Fusar-Poli et al., 2013). Independent of the psychometric instruments used, the mean (95% CI) transition risk to a full psychotic episode has been estimated as follows: 13% (8%-19%) at 6 months of follow-up, 16% after 1 year, 22% after 2 years, and 47% after 3 years, 47% after ≥ 4 years (Fusar-Poli et al., 2012b; Fusar-Poli et al., 2016). Several risk factors have been detected to predict the conversion to psychosis, including the age of ARMS patients (Fusar-Poli et al., 2012b), severity of attenuated positive psychotic symptoms (Oliver et al., 2019), low global functioning (Oliver et al., 2019), severity of negative psychotic symptoms (Oliver et al., 2019), impairments in cognitive func-

tioning (Fusar-Poli et al., 2012c), alterations in structure (Fusar-Poli et al., 2012d; Fusar-Poli et al., 2011), function (Fusar-Poli et al., 2007; Smieskova et al., 2010), connectivity (Crossley et al., 2009) and neurochemistry (Fusar-Poli et al., 2007; Smieskova et al., 2010) of the brain. However, it is still not possible to predict who will transition to psychosis and who will not (Oliver et al., 2019). Antipsychotic medication showed efficacy in reducing the rate of transition to psychosis by 45% (van der Gaag et al., 2013). However, such treatments are associated with high attrition rates (van der Gaag et al., 2013). Thus, the aim of several research projects in this area is to detect potential risk factors that modify risk of transition and improve the identification of patients at risk. Data for this dissertation was obtained from two early detection studies, namely the **FePsy** (**F**rüh**e**rkennung von **Psy**chosen = early detection of psychosis) study and the **EU-GEI** (**EU**ropean network of national schizophrenia networks studying **G**ene-**E**nvironment **I**nteractions) study.

Sex and gender differences

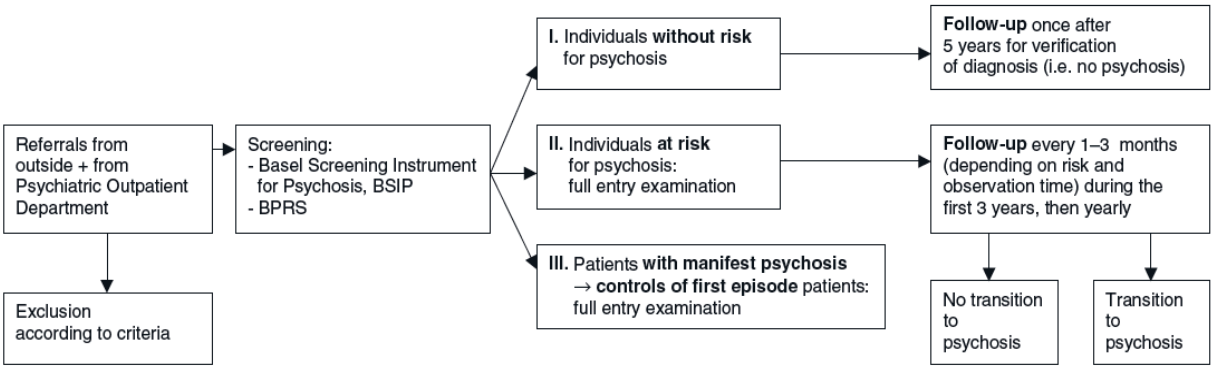
In the last few decades, a growing number of studies have addressed sex and gender differences in almost all areas of health and well-being (Oertelt-Prigione et al., 2012; Riecher-Rössler, 2017; Schiebinger et al., 2016). For example in psychiatry, differences exist regarding prevalence, symptomatology, risk factors and influencing factors or course (Riecher-Rössler, 2010a; Riecher-Rössler, 2017). There is no doubt that sex and gender interact strongly and influence mental well-being as well as psychiatric disorders and diagnoses (Riecher-Rössler, 2010a). However, an import aspect to consider is the conceptual difference of sex and gender. While sex is a biologically reduced and dichotomous term, gender refers to psychosocial and cultural influences (measured by a questionnaire) (Ittig et al., 2015; Riecher-Rössler et al., 2018). Thus far, women are still under-represented in research and several studies still do not report results by sex and/or gender (Riecher-Rössler et al., 2018; Peters et al., 2018). This also applies to schizophrenia research. Only half of all studies on schizophrenia

up to 2010 reported sex and solely 2.5% analysed their findings in relation to sex (Barker-Collo et al., 2011; Riecher-Rössler et al., 2018). This lack of research is surprising since explanations of sex and gender differences may help us to elucidate pathogenic mechanisms that are particular to women or men. Furthermore, such findings would likely improve our treatment and prevention strategies.

FePsy study

The FePsy study is an open prospective clinical study that aims to facilitate and improve the early detection of beginning psychoses (Riecher-Rössler et al., 2007). The study design is presented in Figure 2.

Figure 2. Design of the FePsy study (Riecher-Rössler et al., 2007)



BSIP: Basel Screening Instrument for Psychosis; BPRS: Brief Psychiatric Rating Scale.

Study participants were recruited via the FePsy Clinic at the Psychiatric Outpatient Department of the University Hospital Basel, which aims to identify patients in the early stages of a beginning psychotic disorder and to assess the risk of developing psychosis (Riecher-Rössler et al., 2007). Most referrals came from the own Psychiatric Outpatient Department, which serves an area of about 200 000 inhabitants but there were also some referrals from mental health professionals (e.g. general practitioners, psychiatrists etc.), from relatives or from the subject. All participants were screened with the Basel Screening Instrument for Psychosis

(BSIP) (Riecher-Rössler et al., 2008). The BSIP includes the four psychosis items of the Brief Psychiatric Rating Scale (BPRS, expanded version; Lukoff et al., 1986; Ventura et al., 1993) to rate (pre-) psychotic phenomena. The BSIP criteria corresponds closely to the Personal Assessment and Crisis Evaluation (PACE) inclusion/exclusion criteria (Yung et al., 1998). However, the BSIP additionally permits the inclusion of patients who only exhibit a combination of certain unspecific risk factors and indicators such as prodromes or marked social decline (Riecher-Rössler et al., 2007). For a detailed description of the inclusion/exclusion criteria and the criteria for transition of psychosis, see Riecher-Rössler (2007). All included patients had to undergo an extensive entry examination comprising potential risk factors for transition to psychosis, including systematic assessment of present and previous psychopathology, neuropsychological testing, analyses of different blood parameters and neuroimaging (i.e. resting state electroencephalography [EEG] and structural magnetic resonance imaging [MRI]) (Riecher-Rössler et al., 2007). Each ARMS participant was followed-up at regular intervals for up to 5 years to evaluate whether they transition to frank psychosis (ARMS-T) or not (ARMS-NT). During the first year of follow-up, they were assessed monthly. During the second and third years, they were assessed 3-monthly and thereafter once a year (Riecher-Rössler et al., 2007).

EU-GEI study

The EU-GEI study is a naturalistic prospective multicentre study that aims to identify the interactive genetic, clinical and environmental determinants of schizophrenia (Kraan et al., 2018). Several work packages from multiple disciplines are involved to address the current challenges in Gene-Environment (G × E) research. The general approach and overview of the European Network of National Networks studying Gene-Environment Interactions in Schizophrenia can be found elsewhere (van Os et al., 2014). Study participants were recruited from 11 Early Detection and Intervention Centers: nine in Europe (London, Amsterdam, The

Hague, Vienna, Basel, Cologne, Copenhagen, Paris, Barcelona), one in Brazil (Saõ Paulo), and one in Australia (Melbourne). They were referred to the early detection centers by primary health care services, mental health professionals or from the subject or their family. Control participants were recruited by 4 of the above-mentioned centers: the Institute of Psychiatry, Psychology and Neuroscience (IoPPN) in London, the Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne, the Amsterdam Medical Center (AMC) and Parnassia The Hague. They were approached by telephone and through advertisements at educational institutes. In Melbourne, controls were additionally approached at community centers/noticeboards and advertised via online platforms. All individuals were screened with the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005). The CAARMS was designed to determine if an individual meets ARMS status and to measure other symptoms thought to indicate imminent development of a first-episode psychotic disorder (see Table 1).

Table 1. CAARMS-defined ultra high risk and psychotic disorder threshold criteria (Yung et al., 2005)

UHR status

Group 1: Attenuated psychosis group

(i) Subthreshold intensity:

- Severity scale score of 3–5 on *disorders of thought content* subscale, 3–4 on *perceptual abnormalities* subscale and/or 4–5 on *disorganized speech* subscale of the CAARMS;
- Frequency scale score of 3–6 on *disorders of thought content*, *perceptual abnormalities* and/or *disorganized speech* subscale of the CAARMS for at least 1 week;

OR

- Frequency scale score of 2 on *disorders of thought content*, *perceptual abnormalities* and *disorganized speech* subscale of the CAARMS on more than two occasions.

(ii) Subthreshold frequency:

- Severity scale score of 6 on *disorders of thought content* subscale, 5–6 on *perceptual abnormalities* subscale and/or 6 on *disorganized speech* subscale of the CAARMS;
- Frequency scale score of 3 on *disorders of thought content*, *perceptual abnormalities* and/or *disorganized speech* subscale of the CAARMS;

(for both categories)

- Symptoms present in past year and for not longer than 5 years.

Group 2: BLIPS group:

- Severity scale score of 6 on *disorders of thought content* subscale, 5 or 6 on *perceptual abnormalities* subscale and/or 6 on *disorganized speech* subscale of the CAARMS;
- Frequency scale score of 4–6 on *disorders of thought content*, *perceptual abnormalities* and/or *disorganized speech* subscale;
- Each episode of symptoms is present for less than 1 week and symptoms spontaneously remit on every occasion;
- Symptoms occurred during last year and for not longer than 5 years.

Group 3: Vulnerability:

- Family history of psychosis in first degree relative OR schizotypal personality disorder in identified patient;
- 30% drop in GAF score from premorbid level, sustained for 1 month;
- Change in functioning occurred within last year and maintained at least 1 month.

Psychotic disorder threshold:

- Severity scale score of 6 on *disorders of thought content* subscale, 5 or 6 on *perceptual abnormalities* subscale and/or 6 on *disorganized speech* subscale of the CAARMS;
- Frequency scale score of greater than or equal to 4 on *disorders of thought content*, *perceptual abnormalities* and/or *disorganized speech* subscale;
- Psychotic symptoms present for longer than 1 week.

BLIPS: Brief Limited Intermittent Psychotic Symptoms; CAARMS: Comprehensive Assessment of At-Risk Mental States; GAF: Global Assessment of Functioning; UHR: Ultra High Risk.

A detailed description of the inclusion/exclusion criteria for ARMS and HC can be found in publication 2 of the present dissertation. All participants selected for the study had to undergo a multi-domain assessment at entry including several clinical scales/interviews, neuropsychological testing, analyses of blood parameters and neuroimaging (i.e. MRI). ARMS patients were followed at regular intervals for up to 2 years. Clinical outcome measures were assessed at baseline, 6 months (only brief assessment), 12 months and 24 months after baseline to detect actual transition to psychosis.

Theoretical Background

Sex and gender differences in schizophrenia and emerging psychosis

Sex and gender differences in schizophrenia have been described for many decades. Kraepelin had already reported that women are older at first admission for dementia praecox compared to men (Kraepelin, 1919/1987). This finding has consistently been shown in many studies (Eranti et al., 2013). Differences between men and women with schizophrenia have also been described in other features of the illness, including incidence, prevalence, symptomatology, course and in the response to treatment (Riecher-Rössler et al., 2018; Riecher-Rössler et al., 2010b; Ochoa et al., 2012; Abel et al., 2010). However, findings on sex and gender differences are mostly inconsistent. Many studies suffer from methodological problems, such as different patient groups (FEP, first episode schizophrenia, or chronic patients), confounding effects of antipsychotic medication, a lack of a systematic and homogenous assessment and a lack of statistical power. Furthermore, some results are based on selected help-seeking patient groups rather than on representative populations-based samples. This does not allow drawing valid conclusions on true sex and gender differences (Riecher-Rössler et al., 2018). Therefore, it is essential to describe consistent differences to understand the underlying causes in schizophrenia. The aim of this thesis was to focus on clinical aspects of sex and gender differences in emerging psychosis to better understand the different pathogenesis in women and men leading to psychosis.

Symptomatology, drug use, comorbidity and functioning

Findings regarding gender differences in psychopathological symptoms are less conclusive. It has often been reported that men have more severe negative symptoms, while women show more severe affective and specific psychotic symptoms (Riecher-Rössler et al., 2018). However, many of these studies are based on selected populations rather than on representative community-based populations. In the ABC study, which examined a representative communi-

ty-based sample of first-episode patients, only few gender differences in psychopathology were found, and these were not significant after correction for multiple testing (Häfner et al., 1991; Häfner et al., 1993a). With regard to substance abuse, recent studies in representative first-episode populations suggest that men have a higher prevalence of substance abuse (mainly cannabis and alcohol) (Riecher-Rössler et al., 2018; Abel et al., 2010; Ochoa et al., 2012). It has been assumed that the greater prevalence of substance abuse in men might have contributed to gender differences in symptomatology, which many studies did not control for (Riecher-Rössler et al., 2018). In the general population, there are similar differences in symptomatology between men and women (Seedat et al., 2009). Studies examining gender differences in premorbid and social functioning have found higher functioning in women. This was shown in first-episode psychosis but also during the later course of the disease (Riecher-Rössler et al., 2018; Ochoa et al., 2012).

So far, there are only few methodologically sound studies on gender differences in psychopathology of ARMS individuals. These studies have thus far yielded inconsistent results. In the comprehensive review of Barajas et al. (2015) many studies reported no gender differences in ARMS patients, while others reported more negative symptoms and worse psychosocial functioning in men. A previous study of our own group in ARMS and FEP patients showed more positive psychotic symptoms in women and more negative symptoms in men (Gonzalez-Rodriguez et al., 2014). However, the differences did not withstand correction for multiple testing. More recent studies reported similar small gender differences. While some found more depression and social anxiety (Rietdijk et al., 2013; Pruessner et al., 2017) and more unusual perceptual experiences (Waford et al., 2015) in women, others reported more negative symptoms (Rietschel et al., 2015), disorganized communication (Theodoridou et al., 2019) and violent behaviour (Tseliou et al., 2017) in men. In contrast, no gender differences regarding symptoms were found by Kotlicka-Antczak et al. (2016). However, most of these studies had not corrected for confounding variables or multiple testing. A recent review pub-

lished by Riecher-Rössler et al. (2018) suggests that gender differences in the symptomatology of patients at risk are small and comparable to those seen in the general population. Thus, in a representative worldwide general population sample of 72,933 subjects, men in general had more externalizing and substance disorders, while women had more anxiety and mood disorders (Seedat et al., 2009).

In addition to the at risk signs and symptoms for psychosis, available evidence suggests that many ARMS patients have comorbid nonpsychotic disorders, in particular anxiety disorders and depression (Albert et al., 2018; Fusar-Poli et al., 2014). Fusar-Poli and colleagues (2014) performed a meta-analysis in 1,683 at risk patients and confirmed that baseline prevalence of comorbid depressive and anxiety disorders is 41% and 15%, respectively. To the best of our knowledge, only two studies have investigated gender differences in comorbid depressive and anxiety disorders in ARMS patients at baseline. In a recently conducted study of 764 ARMS patients (women, n = 329; 43%) from the North American Prodrome Longitudinal Study ($NAPLS^{-2}$) a significantly higher lifetime prevalence of depression was observed in women compared to men (64% vs. 56%) (Kline et al., 2018). However, no significant gender differences with respect to depression and anxiety disorders were found in the study of Rietschel et al. (2015).

To further elucidate these issues, the goal of the first study was to investigate gender differences in symptomatology, drug use, comorbidity and global functioning in a large multinational sample of ARMS patients. Based on the above-mentioned previous research, we expected to find no significant differences between ARMS men and women.

Cognitive functioning

The impairment of cognitive functioning is recognized as a core feature of schizophrenia and an important predictor of outcome (Kahn et al., 2013). Several studies have shown that neurocognitive deficits are already present in patients with an ARMS for psychosis (Hauser et al.,

2017; Pflueger et al., 2007). In addition, it has been found that ARMS patients with later transition to psychosis perform worse in tests measuring attention/vigilance, speed of processing, verbal and visual learning, and current and premorbid IC compared to those without transition (Hauser et al., 2017). It has been consistently reported that the prediction of psychosis can be improved by including neurocognitive performance measures into multivariable risk prediction models (Hauser et al., 2017; Studerus et al., 2016; Riecher-Rössler et al., 2009; Riecher-Rössler et al., 2017; Michel et al., 2014).

Sex differences in cognitive functioning are well documented in healthy individuals. In general, women tend to perform better than men in tasks measuring verbal abilities, whereas men outperform women on visual-spatial tasks (Halpern, 2004; Miller et al., 2014; Riecher-Rössler et al., 2018). Similar sex differences regarding neurocognition were found in patients with schizophrenic psychoses (Riecher-Rössler et al., 2018; Mendrek et al., 2016). Many studies have shown that women with schizophrenia have a better performance in verbal learning and memory (Riecher-Rössler et al., 2018; Bozikas et al., 2010; Zhang et al., 2012), whereas men showed a better performance in tests of reaction time, visual memory and executive functions (Riecher-Rössler et al., 2018; Ittig et al., 2015). However, sex differences in cognitive functioning in schizophrenic psychosis remain equivocal. Inconsistencies might partly be due to methodological differences as described previously. Considering ARMS patients, sex differences in cognitive functioning have received considerable attention in recent years. A meta-regression analysis based on 19 studies assessing neuropsychological performance in ARMS patients and HC showed a trend-level significance effect of sex on cognitive performance in ARMS patients, with females performing relatively better than males (Fusar-Poli et al., 2012c). A previous study of our own group found that women perform better in the domain of verbal learning and memory, while men showed a shorter reaction time during the working memory task (Ittig et al., 2015). However, no study has yet investigated sex differences in cognitive functioning in a large multinational sample of ARMS patients by using an extended

neuropsychological battery and a healthy comparison group. We therefore examined sex-related cognitive performance differences in ARMS and HC subjects and whether sex differences vary between the investigated groups. Based on previous research, we expected a better performance of women in the domain of verbal learning and memory irrespective of group.

First self-perceived signs and symptoms

The early prodromal phase of schizophrenia is characterized by unspecific symptoms. Subjects often realize that something is ‘wrong’ – even years before fulfilling diagnostic criteria for a psychotic disorder. During the prodrome, deficits concerning cognition, perception and stress reactivity as well as depressive and negative symptoms have often been reported (Häfner et al., 1998; Häfner et al., 1995a; Iyer et al., 2008). These individually noticed changes will subsequently be referred to as ‘first self-perceived symptoms'. As mentioned above, many studies have investigated the current psychopathological symptoms in ARMS and FEP patients, but only few studies have retrospectively assessed the very first self-perceived symptoms at the onset of the disease. One of the first was the ABC study, which assessed first self-perceived symptoms in FEP patients (using the Instrument for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS)) and found that female FEP patients most frequently reported restlessness, depression and worrying, while men reported trouble with thinking, concentration and anxiety as their initial symptoms (Häfner et al., 1993a, Häfner et al., 1993b). Iyer et al. (2008) examined first self-perceived signs and symptoms retrospectively reported by 128 individuals with first-episode psychosis and found symptoms of depression and anxiety to be the most frequent signs and symptoms. However, the authors did not report any gender-specific early signs and symptoms. An earlier study of our own group compared first self-perceived signs and symptoms independent of gender in ARMS, FEP and depressive disorder patients (Aston et al., 2012). ARMS patients reported ‘loss of energy’ and ‘difficulties concentrating’ as first self-perceived signs and symptoms whereas FEP patients reported

'depression' and 'irritability'. There was much overlap of the first self-perceived signs and symptoms between the three groups.

Although a few studies have retrospectively assessed the very first self-perceived signs and symptoms at illness onset, no study has yet examined ARMS and FEP patients together. Thus, the goal of the third study was to investigate the very first self-perceived signs and symptoms in male and female ARMS and FEP patients. Based on the above-described literature, we hypothesized that overall only small gender differences would be observable in the first self-perceived signs and symptoms of ARMS and FEP patients.

Empirical Studies

Menghini-Müller, S., Studerus, E., Ittig, S., Heitz, U., Egloff, L., Andreou, C., Valmaggia, L. R., Kempton, M. J., van der Gaag, M., de Haan, L., Nelson, B., Barrantes-Vidal, N., Nordentoft, M., Ruhrmann, S., Sachs, G., Rutten, B. P., van Os, J., Riecher-Rössler, A., EU-GEI High Risk Study Group (2019). Gender differences of patients at-risk for psychosis regarding symptomatology, drug use, comorbidity and functioning – Results from the EU-GEI study. European Psychiatry, 59, 52-59.

Menghini-Müller, S., Studerus, E., Ittig, S., Valmaggia L. R., Kempton, M. J., van der Gaag, M., de Haan, L., Nelson, B., Bressan, R. A., Barrantes-Vidal, N., Jantac, C., Nordentoft, M., Ruhrmann, S., Sachs, G., Rutten B. P., van Os, J., Riecher-Rössler, A., EU-GEI High Risk Study Group (2020). Sex differences in cognitive functioning of patients at-risk for psychosis and healthy controls – Results from the EU-GEI study. European Psychiatry, 63(1), e25, 1-9.

Heitz, U., Studerus, E., Menghini-Müller, S., Papmeyer, M., Egloff, L., Ittig, S., Navarra, A., Andreou, C., Riecher-Rössler, A. (2017). Gender differences in first self-perceived signs and symptoms in patients with an at-risk mental state and first-episode psychosis. Early Intervention in Psychiatry, 13(3), 582-588.

Empirical Studies (Manuscript 1)

Gender differences of patients at-risk for psychosis regarding symptomatology, drug use, comorbidity and functioning – Results from the EU-GEI study

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Gender differences of patients at-risk for psychosis regarding symptomatology, drug use, comorbidity and functioning – Results from the EU-GEI study

Stephanie Menghini-Müller[a,b], Erich Studerus[a], Sarah Ittig[a], Ulrike Heitz[a], Laura Egloff[a], Christina Andreou[a], Lucia R. Valmaggia[d], Matthew J. Kempton[c], Mark van der Gaag[e,f], Lieuwe de Haan[g,h], Barnaby Nelson[i], Neus Barrantes-Vidal[j], Merete Nordentoft[k,l], Stephan Ruhrmann[m], Gabriele Sachs[n], Bart P. Rutten[o], Jim van Os[p,q,r], Anita Riecher-Rössler[a,*], EU-GEI High Risk Study Group[1]

[a] Center for Gender Research and Early Detection, University of Basel Psychiatric Hospital, Basel, Switzerland
[b] University of Basel, Department of Psychology, Division of Clinical Psychology and Epidemiology, Basel, Switzerland
[c] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
[d] Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
[e] VU University, Faculty of Behavioural and Movement Sciences, Department of Clinical Psychology and EMGO+ Institute for Health Care Research, Amsterdam, the Netherlands
[f] Parnassia Psychiatric Institute, Department of Psychosis Research, The Hague, the Netherlands
[g] AMC, Academic Psychiatric Centre, Department Early Psychosis, Amsterdam, the Netherlands
[h] Arkin, Amsterdam, the Netherlands
[i] Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia
[j] Departament de Psicologia Clínica I de la Salut (Universitat Autònoma de Barcelona), Fundació Sanitària Sant Pere Claver (Spain), Spanish Mental Health Research Network (CIBERSAM), Spain
[k] Mental Health Center Copenhagen, Mental Health Services in the Capital Region of Denmark, Denmark
[l] Institute for Clinical Medicine, Faculty of Health Science, University of Copenhagen, Denmark
[m] Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany
[n] Medical University of Vienna, Department of Psychiatry and Psychotherapy, Austria
[o] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht, the Netherlands
[p] Department Psychiatry, Brain Centre Rudolf Magnus, Utrecht University Medical Centre, Utrecht, the Netherlands
[q] Department of Psychiatry and Psychology, School for Mental Health and Neuroscience (MHeNS), Maastricht University Medical Centre, Maastricht, the Netherlands
[r] King's College London, King's Health Partners Department of Psychosis Studies, Institute of Psychiatry, London, United Kingdom

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ABSTRACT

Background: Gender differences in symptomatology in chronic schizophrenia and first episode psychosis patients have often been reported. However, little is known about gender differences in those at risk of psychotic disorders. This study investigated gender differences in symptomatology, drug use, comorbidity (i.e. substance use, affective and anxiety disorders) and global functioning in patients with an at-risk mental state (ARMS) for psychosis.
Methods: The sample consisted of 336 ARMS patients (159 women) from the prodromal work package of the EUropean network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI; 11 centers). Clinical symptoms, drug use, comorbidity and functioning were assessed at first presentation to an early detection center using structured interviews.
Results: In unadjusted analyses, men were found to have significantly higher rates of negative symptoms and current cannabis use while women showed higher rates of general psychopathology and more often displayed comorbid affective and anxiety disorders. No gender differences were found for global functioning. The results generally did not change when corrected for possible cofounders (e.g. cannabis

* Corresponding author at: University of Basel Psychiatric Hospital, Center for Gender Research and Early Detection, Wilhelm Klein-Strasse 27, 4002 Basel, Switzerland.
E-mail address: anita.riecher@upk.ch (A. Riecher-Rössler).
[1] A full list of authors and affiliations appears in the Appendix.

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use). However, most differences did not withstand correction for multiple testing.
Conclusions: Findings indicate that gender differences in symptomatology and comorbidity in ARMS are similar to those seen in overt psychosis and in healthy controls. However, observed differences are small and would only be reliably detected in studies with high statistical power. Moreover, such small effects would likely not be clinically meaningful.

1. Introduction

Gender differences in schizophrenia have attracted the attention of scientific research for more than a century. Kraepelin had already reported that women are older at first admission for dementia praecox compared to men [1]. Most studies to date confirm these findings [2]. Findings on severity of psychopathological symptoms are less conclusive, with some authors suggesting that men have more severe negative symptoms while women show more severe affective and specific psychotic symptoms [2]. However, only few gender differences in psychopathology of first episode schizophrenia were found in the ABC study, and these were not significant after correction for multiple testing [3,4]. With regard to substance abuse, available evidence suggests that men have a higher prevalence of substance abuse and higher levels of comorbidity compared to women. Additionally, studies examining gender differences in premorbid and social functioning have found higher functioning in women [2].

In the past two decades, the field of early detection of psychosis has received growing scientific and clinical interest [5], albeit that only few methodologically sound studies have considered gender differences in patients with an at-risk mental state (ARMS) for psychosis. These studies have thus far yielded inconsistent results. With regard to symptomatology, most studies described in the comprehensive review of Barajas et al. [6] reported no gender differences in ARMS patients. Nevertheless, some studies found more severe negative symptoms in men, and other studies found lower levels of social functioning and a longer duration of untreated illness in men compared to women [6]. A more recent review published by Riecher-Rössler et al. [2] suggests that gender differences in the symptomatology of patients at risk are small and comparable to those seen in the general population. Thus, in a representative worldwide general population sample of 72,933 subjects, men in general had a greater propensity to substance, alcohol and cannabis abuse, while women had more affective symptoms, depression and anxiety [7].

In addition to the at-risk signs and symptoms for psychosis, many ARMS patients suffer from comorbid non-psychotic mental disorders, in particular depression and anxiety disorders [8,9]. To our knowledge, only two studies have investigated gender differences in comorbid depressive and anxiety diagnoses in ARMS patients at baseline. Kline et al. [10] examined a cohort of 764 ARMS patients (women, n = 329; 43%) from the North American Prodrome Longitudinal Study (NAPLS^{-2}), and observed a significantly higher lifetime prevalence of depression in women than men (64% vs. 56%). No significant gender differences in comorbid affective and anxiety disorders were observed in the study of Rietschel et al. [11].

To further elucidate these issues, the present study investigated gender differences in symptomatology, drug use, comorbidity (i.e. substance use, affective and anxiety disorders) and global functioning in a large multinational sample of ARMS patients. Based on previous and our own findings, we expected to find no significant differences between ARMS men and women.

2. Methods

2.1. Setting and recruitment

The data analysed in this study were collected within the multicenter EUropean Gene-Environment Interactions (EU-GEI) study, from May 1, 2010 to April 30, 2015. The aim of EU-GEI study is to identify the interactive genetic, clinical and environmental determinants of schizophrenia [12]. The overall design of the study was naturalistic, longitudinal and prospective, consisting of a baseline and two follow-up time points. For the current analyses, only baseline, i.e. at intake into the study, data were used and only patients with complete data on cannabis frequency were included.

ARMS patients were recruited from 11 Early Detection and Intervention Centers, nine in Europe (London, Amsterdam, The Hague, Vienna, Basel, Cologne, Copenhagen, Paris, Barcelona), one in Brazil (Saõ Paulo), and one in Australia (Melbourne). Referrals were accepted from primary health care services, mental health professionals, or from the subject or their family. Study intake corresponds to the admission date in the early detection service. All participants were screened with an inclusion/exclusion checklist (see below).

The protocol of the EU-GEI study was approved by the institutional review boards of all study sites. EU-GEI was conducted in accordance with the Declaration of Helsinki. The Medical Ethics Committees of all participating sites approved the study protocol.

2.2. Inclusion and exclusion criteria

Inclusion criteria for EU-GEI were: aged 18–35; being at-risk for psychosis as defined by the Comprehensive Assessment of At-Risk Mental State (CAARMS) [13]; adequate language skills local to each center; and consent to study participation.

The exclusion criteria were: prior experience of a psychotic episode of more than 1-week as determined by the CAARMS [13] and Structural Clinical Interview for DSM Disorders (SCID) [14]; previous treatment with an antipsychotic for a psychotic episode; and IQ < 60.

2.3. Determination of ARMS status

The CAARMS, used to identify ARMS patients [13], is a semi-structured interview that encompasses psychotic symptoms and a range of other psychopathological symptoms occurring in emerging psychotic disorder. Individuals were classified as being in an ARMS for psychosis if they met at least one of the following risk criteria: (i) Vulnerability Group (a first-degree relative with a psychotic disorder or diagnosed with schizotypal personality disorder in combination with a significant drop in functioning); (ii) Attenuated Psychotic Symptoms (APS) (psychotic symptoms sub-threshold either in intensity or frequency); (iii) Brief Limited Psychotic Symptoms (BLIPS) (recent episode of brief psychotic symptoms that spontaneously resolved within 1 week). The full criteria can be found in Yung et al. [13].

2.4. Assessment of sociodemographic characteristics and medication

Sociodemographic characteristics were obtained using the modified Medical Research Council (MRC) sociodemographic schedule [15]. Data on psychiatric medication were assessed with a medical history questionnaire, designed by the EU-GEI group.

2.5. Assessment of psychopathology

Psychopathological symptoms were assessed using the expanded version of the Brief Psychiatric Rating Scale (BPRS-E) [16], the Scale for the Assessment of Negative Symptoms (SANS) [17], the Comprehensive Assessment of At-Risk Metal State (CAARMS) [13], the Montgomery-Åsberg Depression Rating Scale (MADRS) [18], and the Young Mania Rating Scale (YMRS) [19]. Genders differences were investigated using the following subscales:

BPRS-E: Activation, Positive symptoms, Negative symptoms, Affect, Disorganization as defined by Shafer et al. [16] and the total score

SANS: Affective Flattening, Alogia, Asociality-Anhedonia, Avolition-Apathy, Inattention and the total score [17]

CAARMS: Behavioral change, Cognitive change - attention/concentration, Emotional disturbance, Motor/physical changes, Negative symptoms, Positive symptoms, General Psychopathology[20]

MADRS: Detachment, Negative Thoughts, Neurovegetative, Sadness as defined by Quilty et al. [21] and the total score

YMRS: Total score [19]

2.6. Assessment of comorbidity, drug use and functioning

Affective and anxiety disorders were assessed with the Structured Clinical Interview for the Diagnostic Manual of Psychiatric Disorders-IV (DSM-IV/SCID) [14]. Current use, abuse and dependence of cannabis, amphetamine (e.g. speed, ecstasy), cocaine, and hallucinogens (e.g. lysergic acid diethylamide (LSD), “magic mushrooms”) were assessed using the Cannabis Experience Questionnaire [22]. For cannabis, the frequency of use was additionally assessed. Participants were defined as being current users of a substance if they identified themselves as such or if they reported any use in the preceding month.

The general level of functioning was assessed with the GAF scale [23].

2.7. Statistical analyses

All statistical analyses were carried out using R environment for statistical computing [24]. Because observations were non-independent, that is, observations from the same center were more similar than observations from different centers, gender differences were analysed using mixed effects models including gender as a fixed effects factor and randomly varying intercepts per center to account for the clustering in the data. We used linear mixed effects models for continuous measures (i.e. age, years of education, functioning and psychopathology scales), mixed effects logistic regression models for binary measures (i.e. psychiatric diagnoses, drug use and psychiatric medication), ordinal mixed effects models for ordered categorical measures (i.e. cannabis frequency and highest level of education) and mixed effects multinomial logistic regression for unordered categorical measures (i.e. living situation). We analysed gender differences in the frequency of use of antipsychotics, antidepressants and hypnotics. Cannabis frequency and age were included as covariates in models estimating gender differences in psychopathology and living situation, respectively. Continuous dependent variables were z-transformed before inclusion to models and gender was included as a binary variable with 0 and 1 describing men and women, respectively. Thus, the regression coefficient for gender described the standardized mean difference of women compared to men. *P*-values were adjusted for multiple testing across all of the 63 gender differences tests using the False Discovery Rate (FDR) procedure [25].

3. Results

3.1. Sample description

In total, 345 ARMS patients participated in the EU-GEI study. The sample of this study consisted of 336 ARMS patients (177 men, 159 women). 9 ARMS patients had not complete data on cannabis frequency and were excluded. Sociodemographic and clinical characteristics are presented in Table 1. Male patients were significantly older than female patients in unadjusted analyses ($P = 0.011$). The significance of this effect disappeared after correction for multiple testing ($P = 0.175$). There were no significant gender differences in ARMS patients with regard to years of education, highest level of education, living situation and current psychiatric medication.

Table 1
Sociodemographic and clinical characteristics.

	Men (n = 177)	Women (n = 159)	N	*P*-value uncorrected	*P*-value corrected[a]
Age	22.8 (5.13)	22.0 (4.70)	336	0.011*	0.175
Years of education	14.4 (3.29)	14.4 (2.84)	301	0.190	0.471
Highest level of education			296	0.987	1.000
School, no qualifications	16 (9.88%)	11 (8.21%)			
School, with qualifications	51 (31.5%)	47 (35.1%)			
Tertiary, Further	50 (30.9%)	38 (28.4%)			
Vocational	24 (14.8%)	17 (12.7%)			
Higher (undergraduate)	18 (11.1%)	17 (12.7%)			
Higher (postgraduate)	3 (1.85%)	4 (2.99%)			
Living with			336	0.575	0.471[b]
Alone	28 (15.8%)	23 (14.5%)			
Other	56 (31.6%)	61 (38.4%)			
Parents/family	93 (52.5%)	75 (47.2%)			
Antipsychotics currently	15 (10.3%)	15 (11.3%)	279	0.911	0.988
Antidepressants currently	41 (28.1%)	43 (32.3%)	279	0.909	0.988
Hypnotics currently	2 (1.37%)	2 (1.50%)	279	0.994	1.000

Continuous variables are described by means and standard deviations in parentheses.
[a] *P*-value corrected for multiple testing.
[b] *P*-value corrected for age and multiple testing.
* $P < 0.05$.

3.2. Gender differences in symptomatology and functioning

Table 2 shows the results of the linear mixed effects models using symptomatology as continuous dependent variable and gender as fixed effects factor. Standardized mean differences (SMD) and 95% confidence intervals of the psychopathological syndrome scales are additionally presented in Fig. 1.

Female ARMS patients showed significantly less severe BPRS "Negative Symptoms" (b = −0.22, P = 0.046), more CAARMS "General psychopathology" (b = 0.30, P = 0.007) and trendwise less SANS "Affective Flattening" (b = −0.20, P = 0.073) than male ARMS patients in uncorrected analyses. These differences became significant when corrected for cannabis use (BPRS: b = −0.24, P = 0.032; CAARMS: b = 0.33, P = 0.003, SANS: b = −0.22, P = 0.048). However, when p-values were additionally adjusted for multiple testing by using the FDR procedure, differences in negative symptoms and general psychopathology were no longer significant. There were no gender differences in ARMS patients with regard to global functioning.

3.3. Gender differences in drug use and comorbidity

Table 3 shows the ORs for associations of gender with comorbid drug use and affective and anxiety disorders for ARMS patients at

Table 2
Gender differences in psychopathology and functioning.

Rating scale	Men (n = 177)	Women (n = 159)	N	Coefficient [CI] uncorrected	Coefficient [CI] corrected cannabis use	*P*-value uncorrected	*P*-value corrected for cannabis use	*P*-value fully corrected[a]
BPRS								
BPRS Activation	3.8 (1.7)	3.5 (1.3)	319	−0.15 [-0.37; 0.07]	−0.10 [-0.32; 0.12]	0.191	0.396	0.700
BPRS Affect	7.7 (3.2)	8.1 (3.1)	319	0.02 [-0.20; 0.25]	0.06 [-0.16; 0.29]	0.848	0.613	0.866
BPRS Disorganization	4.0 (1.5)	3.6 (1.3)	319	−0.13 [-0.35; 0.09]	−0.09 [-0.32; 0.13]	0.241	0.412	0.700
BPRS Negative Symptoms	5.4 (2.7)	4.7 (2.0)	319	−0.22 [-0.44; -0.01]	−0.24 [-0.46; -0.02]	0.046*	0.032*	0.181
BPRS Positive Symptoms	7.7 (3.3)	7.3 (3.0)	318	−0.09 [-0.31; 0.12]	−0.05 [-0.27; 0.17]	0.406	0.663	0.886
BPRS total score	44.2 (10.8)	43.0 (9.7)	319	−0.07 [-0.29; 0.14]	−0.03 [-0.24; 0.19]	0.498	0.798	0.928
CAARMS								
CAARMS Behavioral change	7.8 (4.2)	8.2 (3.7)	332	0.07 [-0.15; 0.30]	0.11 [-0.11; 0.33]	0.520	0.336	0.700
CAARMS Cognitive change, attention/concentration	3.2 (1.8)	3.1 (1.8)	332	0.03 [-0.20; 0.25]	0.04 [-0.19; 0.26]	0.804	0.740	0.925
CAARMS Emotional disturbance	3.2 (2.3)	3.1 (2.5)	330	−0.02 [-0.24; 0.20]	−0.04 [-0.26; 0.18]	0.862	0.751	0.925
CAARMS General psychopathology	13.8 (6.6)	16.1 (6.0)	333	0.30 [0.08; 0.52]	0.33 [0.12; 0.56]	0.007**	0.003**	0.087
CAARMS Motor/physical changes	2.1 (2.7)	2.3 (2.5)	329	0.18 [-0.04; 0.40]	0.19 [-0.03; 0.41]	0.107	0.088	0.312
CAARMS Negative symptoms	6.7 (3.7)	7.2 (3.1)	331	0.10 [-0.11; 0.34]	0.12 [-0.10; 0.35]	0.347	0.298	0.700
CAARMS Positive symptoms	10.0 (3.9)	9.7 (4.4)	334	0.00 [-0.21; 0.21]	0.02 [-0.20; 0.23]	0.993	0.862	0.985
GAF								
GAF Disability, impairment	55.6 (12.4)	55.2 (12.4)	328	0.05 [-0.18; 0.26]	0.01 [-0.22; 0.22]	0.682	0.960	1.000
GAF Symptoms	54.9 (10.3)	55.3 (10.1)	313	0.07 [-0.16; 0.29]	0.05 [-0.18; 0.28]	0.570	0.678	0.886
MADRS								
MADRS Detachment	6.4 (3.2)	6.2 (3.2)	323	−0.07 [-0.29; 0.15]	−0.07 [-0.29; 0.16]	0.546	0.568	0.846
MADRS Negative Thoughts	3.0 (2.3)	3.2 (2.1)	322	0.07 [-0.15; 0.31]	0.10 [-0.12; 0.35]	0.528	0.374	0.700
MADRS Neurovegetative	5.0 (3.1)	5.4 (3.3)	323	0.14 [-0.09; 0.36]	0.17 [-0.06; 0.39]	0.228	0.147	0.410
MADRS Sadness	4.2 (2.7)	4.4 (2.8)	323	0.03 [-0.19; 0.26]	0.03 [-0.19; 0.26]	0.759	0.773	0.927
MADRS total score	18.6 (9.3)	19.2 (9.1)	323	0.06 [-0.16; 0.28]	0.08 [-0.14; 0.31]	0.581	0.464	0.724
SANS								
SANS Affective Flattening	4.0 (4.7)	2.9 (4.2)	325	−0.20 [-0.42; 0.02]	−0.22 [-0.45; 0.00]	0.073	0.048*	0.238
SANS Alogia	1.8 (2.5)	1.0 (2.1)	325	−0.17 [-0.38; 0.04]	−0.17 [-0.39; 0.04]	0.120	0.121	0.381
SANS Asociality-Anhedonia	6.1 (4.6)	5.1 (4.0)	324	−0.16 [-0.39; 0.06]	−0.18 [-0.41; 0.05]	0.157	0.125	0.381
SANS Avolition-Apathy	3.5 (2.9)	3.4 (2.6)	325	0.06 [-0.15; 0.27]	0.08 [-0.13; 0.30]	0.576	0.449	0.724
SANS Inattention	0.9 (1.5)	1.1 (1.7)	321	0.20 [-0.02; 0.41]	0.20 [-0.02; 0.41]	0.069	0.079	0.312
SANS total score	16.4 (11.5)	13.5 (10.8)	325	−0.14 [-0.35; 0.08]	−0.15 [-0.37; 0.07]	0.216	0.191	0.471
YMRS								
YMRS total score	4.4 (5.1)	3.3 (3.8)	316	−0.17 [-0.38; 0.05]	−0.09 [-0.30; 0.12]	0.131	0.415	0.700

BPRS: Brief Psychiatric Rating Scale; CAARMS: Comprehensive Assessment of At-Risk Mental State; GAF: Global Assessment of Functioning; MADRS: Montgomery Åsberg Depression Rating Scale;
SANS: Scale for the Assessment of Negative Symptoms; YMRS: Young Mania Rating Scale; CI = 95% Confidence Interval.
[a] *P*-value corrected for cannabis use and multiple testing.
* $P < 0.05$.
** $P < 0.01$.

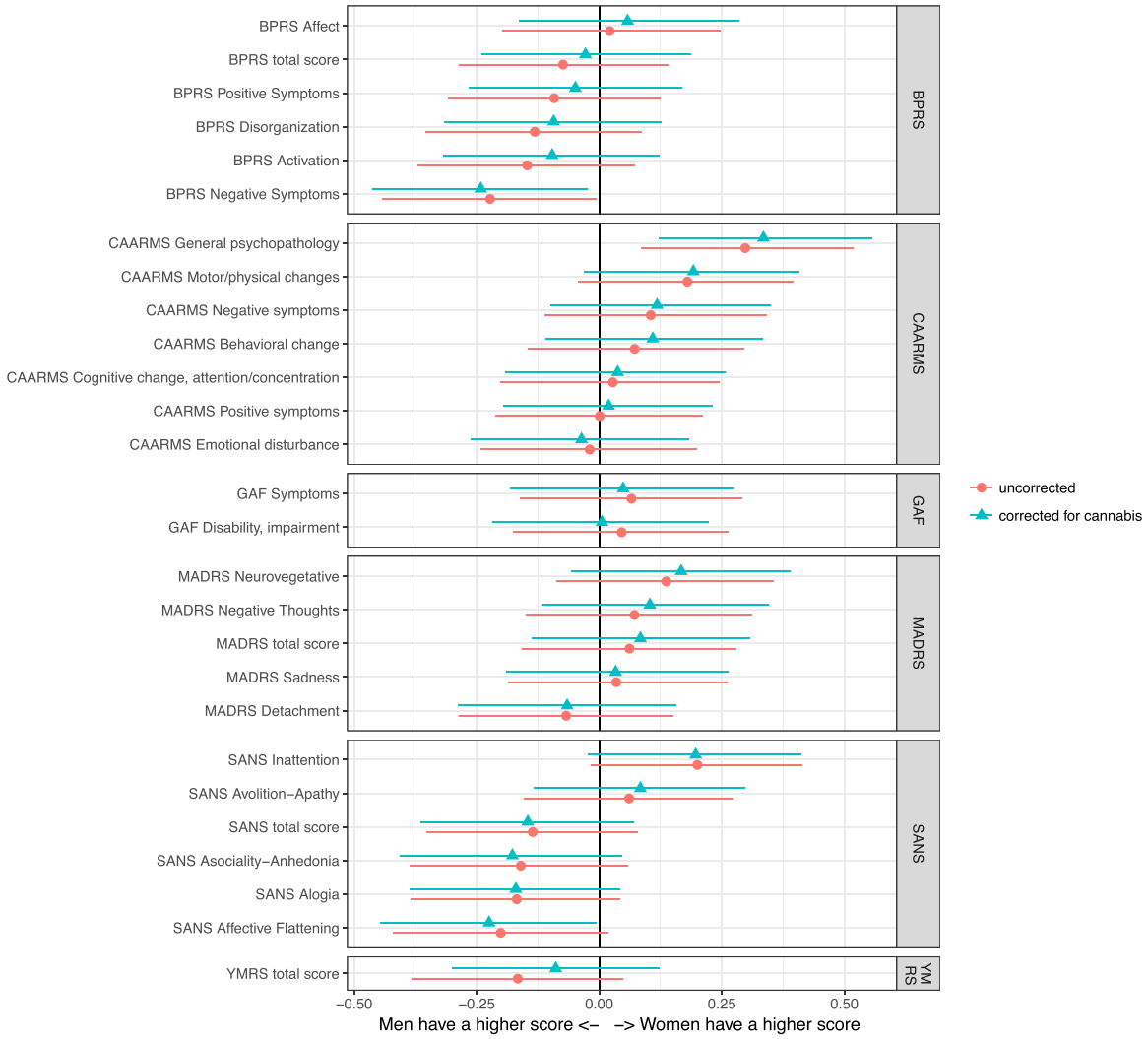

Fig. 1. Standardized mean differences (*d*) and 95% confidence intervals of the Brief Psychiatric Rating Scale (BPRS), Comprehensive Assessment At-Risk Mental State (CAARMS), Global Assessment of Functioning (GAF), Montgomery-Åsberg Depression Rating Scale (MADRS), Scale for the Assessment of Negative Symptoms (SANS) and Young Mania Rating Scale (YMRS). The bold vertical line at zero represents the severity of symptomatology in men. Differences are significant if the 95% confidence interval (horizontal line) does not overlap with zero.

baseline. Unadjusted ORs indicate that men had a significantly higher proportion of current cannabis users (OR, 0.53; 95% CI 0.32 to 0.88; $P = 0.015$) and a higher current frequency of cannabis use than women ($P = 0.008$).

With regard to broad diagnostic categories, women were significantly more often diagnosed with any lifetime affective disorder (OR, 1.72; 95% CI 1.05–2.81; $P = 0.032$) and any current anxiety disorder (OR, 1.66; 95% CI 1.04–2.64; $P = 0.034$). With regard to specific diagnoses, women were more frequently diagnosed with a past major depressive episode (OR, 1.78; 95% CI 1.11–2.88; $P = 0.018$), a current panic disorder with (OR, 2.57; 95% CI 1.14–5.81; $P = 0.024$) and without agoraphobia (OR, 2.00; 95% CI 1.12–3.55; $P = 0.019$), current specific phobia (OR, 4.26; 95% CI 1.90–9.51; $P = < 0.001$) and current PTSD (OR, 2.25; 95% CI 1.07–4.74; $P = 0.033$). However, when adjusted for multiple testing, only current specific phobia remained significantly associated with gender ($P = 0.031$).

4. Discussion

The current study investigated gender differences in socio-demographic variables, symptomatology, drug use, comorbidity (i.e. substance use, affective and anxiety disorders) and global functioning in 336 ARMS patients presenting for the first time at an early detection service in a multi-national study. Unadjusted analyses indicated higher severity of negative symptoms (i.e. BPRS negative symptoms, SANS affective flattening) and current cannabis use in men while women showed higher severity of general psychopathology (CAARMS) and suffered more from comorbid affective (i.e. lifetime affective disorders, past major depressive episode) and anxiety disorders (e.g. panic, panic with agoraphobia, specific phobia, PTSD). However, when corrected for multiple testing and confounding variables, these differences were no longer significant except for higher lifetime rates of specific phobia in women.

Regarding sociodemographic variables, our results are in agreement with an earlier study on ARMS patients [11] with the exception of age and living situation. While Rietschel et al. [11] found no gender difference in age, the current study found male ARMS patients to be significantly older than female ARMS patients but only if statistically not corrected for multiple testing. Rietschel et al. [11] suggest that male ARMS patients are living more frequently with their parents or other relatives than female ARMS patients whereas the present study did not find any significant

Table 3
Gender differences in drug use and comorbidity.

SCID Diagnosis	Men (n = 177)	Women (n = 159)	N	Odds ratio [CI]	*P*-value uncorrected	*P*-value corrected[a]
Drug use						
Cannabis current use	56 (31.6%)	31 (19.5%)	336	0.53 [0.32; 0.88]	0.015*	0.175
Cannabis current frequency			336		0.008**	0.168
none	121 (68.4%)	128 (80.5%)				
only once or twice	2 (1.13%)	2 (1.26%)				
a few times each year	7 (3.95%)	10 (6.29%)				
a few times each month	12 (6.78%)	5 (3.14%)				
(more than) once a week	9 (5.08%)	2 (1.26%)				
every day	26 (14.7%)	12 (7.55%)				
Cannabis lifetime dependence	36 (35.6%)	21 (26.9%)	179	0.72 [0.38; 1.40]	0.337	0.714
Amphetamines current use	30 (26.1%)	17 (21.0%)	196	0.74 [0.37; 1.46]	0.383	0.721
Amphetamines current abuse	2 (1.7%)	2 (2.5%)	196	1.43 [0.20; 10.48]	0.725	0.910
Amphetamines current dependence	2 (1.7%)	3 (3.7%)	196	2.23 [0.42; 11.97]	0.351	0.714
Cocaine current use	28 (24.3%)	11 (13.6%)	196	0.49 [0.23; 1.05]	0.069	0.312
Cocaine current abuse	2 (1.7%)	2 (2.5%)	196	1.52 [0.39; 5.84]	0.544	0.808
Cocaine current dependence	2 (1.7%)	1 (1.2%)	196	0.69 [0.16; 2.98]	0.619	0.829
Hallucinogens current use	16 (13.9%)	9 (11.1%)	196	0.81 [0.34; 1.89]	0.622	0.829
Hallucinogens current abuse	1 (0.9%)	1 (1.2%)	196	1.71 [0.42; 6.96]	0.456	0.788
Hallucinogens current dependence	1 (0.9%)	0 (0.0%)	196	0.00 [0.00; 0.00]	1.000	1.000
Affective disorders						
Lifetime affective disorder	106 (59.9%)	122 (76.7%)	336	1.72 [1.05; 2.81]	0.032*	0.198
Current major depressive episode	48 (27.6%)	59 (38.6%)	327	1.52 [0.93; 2.46]	0.093	0.329
Past major depressive episode	71 (41.8%)	84 (57.5%)	316	1.78 [1.11; 2.88]	0.018*	0.175
Current dysthymic disorder	10 (6.0%)	10 (6.7%)	317	0.89 [0.37; 2.10]	0.782	0.945
Past manic episode	5 (3.0%)	7 (4.7%)	319	1.64 [0.54; 5.00]	0.385	0.721
Current hypomaniac episode	3 (1.9%)	1 (0.7%)	306	0.37 [0.04; 3.63]	0.395	0.721
Past hypomaniac episode	8 (4.8%)	9 (6.1%)	314	1.24 [0.47; 3.26]	0.665	0.868
Anxiety disorders						
Current anxiety disorder	71 (40.1%)	94 (59.1%)	336	1.66 [1.04; 2.64]	0.034*	0.198
Current panic disorder	26 (15.7%)	44 (29.5%)	315	2.00 [1.12; 3.55]	0.019*	0.175
Current panic disorder with agoraphobia	9 (5.9%)	21 (15.3%)	290	2.57 [1.14; 5.81]	0.024*	0.194
Current agoraphobia without history of panic disorder	3 (1.7%)	3 (1.9%)	336	0.90 [0.18; 4.53]	0.895	0.988
Current social phobia	23 (13.6%)	38 (25.5%)	318	1.66 [0.92; 3.01]	0.092	0.329
Current specific phobia	7 (4.2%)	29 (19.3%)	318	4.26 [1.90; 9.51]	<0.001***	0.031*
Current generalized anxiety disorder	14 (8.5%)	22 (14.6%)	315	1.69 [0.84; 3.40]	0.144	0.419
Current obsessive compulsive disorder	16 (10.3%)	13 (9.3%)	295	0.99 [0.46; 2.13]	0.987	1.000
Current post traumatic stress disorder	11 (6.6%)	23 (15.3%)	317	2.25 [1.07; 4.74]	0.033*	0.198

SCID: Structured Clinical Interview for the Diagnostic Manual of Psychiatric Disorders DSM-IV; CI: 95% Confidence Interval.
[a] *P*-value corrected for multiple testing.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

gender differences. This finding may be due to the slightly lower average age in our sample. Another possibility is that this gender difference is dependent on the country or region the sample is taken from.

Regarding psychopathology, our findings were in line with a previous study of our own group that reported no gender differences in psychopathology, neither in ARMS nor in FEP patients, when corrected for multiple testing [26]. Furthermore, Willhite et al. [27] also found no significant gender differences in ratings of any of the symptoms of the Scale of Prodromal Symptoms (SOPS) in high-risk patients. A possible explanation may be that gender differences in the symptoms are so small that they can only be reliably detected in studies with very high statistical power (i.e. in very large datasets or in meta-analyses). However, such small effects would likely not be clinically meaningful.

Regarding drug use and comorbidity, male ARMS patients showed higher rates of current cannabis use and frequency of intake in unadjusted but not in adjusted analyses compared to female ARMS patients. This finding is in line with a previous study of our own group [26] and others that report no gender differences regarding substance abuse in the prodromal phase of schizophrenia [2]. However, higher rates of substance abuse in men are found in the general population [7] and in schizophrenia in particular [2].

Our finding of higher rates of comorbid affective and anxiety disorders in female ARMS patients contradicts a recent study on ARMS patients, which has found no gender differences for affective and anxiety disorders [11]. However, an earlier study found greater rates of current depression and social anxiety in high-risk women compared to men [28]. Furthermore, Pruessner et al. [29] also found more depressive symptoms in high-risk women, but these differences did not withstand correction for multiple testing. An explanation may be that the self-report questionnaires used in the study of Rietdijk et al. [28] have led to an overestimation of the number of patients with an anxiety disorder or depression. Most importantly, our results are in line with epidemiological studies on depression and anxiety in the general population, which found female/male prevalence ratios of 2:1, respectively [30,31]. ARMS patients in this respect thus do not seem to differ from the general population.

Our finding of no gender difference in terms of level of functioning is in accordance with previous studies [2].

A strength of our study is that we examined gender differences with several, well established instruments to assess a broad range of symptomatology. Rater trainings have been used to ensure that all raters administering the rating scales in the same way. Furthermore, the multicentre design of our study might have contributed to heterogeneity in our sample through, for example,

different cultural modes of expression and accessibility and potency of cannabis products in different study centres. We have therefore included random intercepts that varied across study centres in all our models. Finally, this is one of the first studies to investigate gender differences in symptomatology in an ARMS sample of this size.

However, although data were collected by well-trained interviewers using standardized questionnaires and well-established diagnostic criteria, this does not completely eliminate possible gender-specific biases, e.g. of questionnaires and interviewing techniques, of self-reporting, or interpreting patient information, of applying diagnostic criteria or attributing diagnostic labels [32]. Furthermore, this study concentrates on the age group of 18–35 years with the consequence that especially boys, who are at-risk state presumably before age 18 and women with later age of onset are missed. An additional limitation could be that our sample may not be representative for the overall population of help-seeking patients since we do not know whether all ARMS patients in the relevant catchment areas were searching help and came to an early detection service. A recent study found a significantly different gender distribution between ARMS and first episode psychosis (FEP) patients with a greater proportion of males in FEP cohorts than in clinical high-risk cohorts [33]. The authors presume that ARMS men are probably less likely to be help-seeking or less 'literate' of symptoms of mental illness which could lead to an under-representation of men in existing clinical high-risk services. Lastly, it should be noted that ARMS patients represent a heterogeneous patient group with only about 20–35% developing frank psychosis [34,35] and about one third having a clinical remission within the first two years of the follow-up [36]. Hence, gender differences reported in this study cannot be generalized to patients being in true prodromal state for psychosis.

Taken together, our findings indicate that gender differences in symptomatology – if present at all – are so small that they are likely not to be clinically meaningful.

Disclosure of interest

All authors declare not to have any conflicts of interest that might be interpreted as influencing the content of the manuscript.

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Apppendix A

EU-GEI High Risk Study Group – Author List

Philip McGuire[2], Lucia R. Valmaggia[3], Matthew J. Kempton[2], Maria Calem[2], Stefania Tognin[2], Gemma Modinos[2], Lieuwe de Haan[4,7], Mark van der Gaag[8,10], Eva Velthorst[5,11], Tamar C. Kraan[6], Daniella S. van Dam[4], Nadine Burger[7], Barnaby Nelson[12,13], Patrick McGorry[12,13], G Paul Amminger[12,13], Christos Pantelis[14], Athena Politis[12,13], Joanne Goodall[12,13], Anita Riecher-Rössler[1], Stefan Borgwardt[1], Charlotte Rapp[1], Sarah Ittig[1], Erich Studerus[1], Renata Smieskova[1], Rodrigo Bressan[15], Ary Gadelha[15], Elisa Brietzke[16], Graccielle Asevedo[15], Elson Asevedo[15], Andre Zugman[15], Neus Barrantes-Vidal[17], Tecelli Domínguez-Martínez[18], Anna Racioppi[19], Paula Cristóbal-Narváez[19], Thomas R. Kwapil[20], Manel Monsonet[19], Mathilde Kazes[21], Claire Daban[21], Julie Bourgin[21], Olivier Gay[21], Célia Mam-Lam-Fook[21], Marie-Odile Krebs[21], Dorte Nordholm[22], Lasse Randers[22], Kristine Krakauer[22], Louise Glenthøj[22], Birte Glenthøj[23], Merete Nordentoft[22], Stephan Ruhrmann[24], Dominika Gebhard[24], Julia Arnhold[25], Joachim Klosterkötter[24], Gabriele Sachs[26], Iris Lasser[26], Bernadette Winklbaur[26], Philippe A. Delespaul[27,28], Bart P. Rutten[29], and Jim van Os[29,30]

Affiliations

[1] University Psychiatric Hospital, Wilhelm Klein-Strasse 27, CH-4002 Basel, Switzerland; [2] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark 458 Hill, London, United Kingdom SE5 8AF; [3] Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark Hill, 456 London, United Kingdom SE5 8AF; [4] Amsterdam UMC, University of Amsterdam, Psychiatry, Department Early Psychosis, Meibergdreef 9, Amsterdam, The Netherlands; [5] Department of Psychiatry and Seaver Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, NY, US; [6] Mental Health Institute Arkin, Amsterdam, the Netherlands; [7] Arkin Amsterdam; [8] VU University, Faculty of Behavioural and Movement Sciences, Department of Clinical Psychology and Amsterdam Public Mental Health research institute, van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands; [9] Mental Health Institute Noord-Holland Noord, Hoorn, the Netherlands; [10] Parnassia Psychiatric Institute, Department of Psychosis Research, Zoutkeetsingel 40, 2512 HN The Hague, The Netherlands; [11] Early Psychosis Section, Department of Psychiatry, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; [12] Orygen, The National Centre of Excellence in Youth Mental Health, University of Melbourne; [13] Centre for Youth Mental Health, University of Melbourne, 35 Poplar Road (Locked Bag 10), Parkville, Victoria 485 3052, Australia; [14] Melbourne Neuropsychiatry Centre, The University of Melbourne; [15] LiNC - Lab Interdisciplinar Neurociências Clínicas, Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP; [16] Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP; [17] Departament de Psicologia Clínica i de la Salut (Universitat Autònoma de Barcelona), Fundació Sanitària Sant Pere Claver (Spain), Spanish Mental Health Research Network (CIBERSAM); [18] CONACYT-Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz (México); [19] Departament de Psicologia Clínica i de la Salut (Universitat Autònoma de Barcelona); [20] Department of Psychology, University of Illinois at Urbana-Champaign (USA); [21] University Paris Descartes, Hôpital Sainte-Anne, C'JAAD, Service Hospitalo-Universitaire, Inserm U894, Institut de Psychiatrie (CNRS 3557) Paris, France; [22] Mental Health Center Copenhagen and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, Mental Health Center Glostrup, Mental Health Services in the Capital Region of Copenhagen, University of Copenhagen; [23] Centre for Neuropsychiatric Schizophrenia Research (CNSR) & Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark; [24] Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany; [25] Psyberlin, Berlin, Germany; [26] Medical University of Vienna, Department of Psychiatry and Psychotherapy; [27] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, P.O. Box 616, 6200 MD 464 Maastricht, The Netherlands; [28] Mondriaan Mental Health Trust, P.O. Box 4436 CX Heerlen, The Netherlands; [29] Medical University of Vienna,

Department of Psychiatry and Psychotherapy; [30] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, Denmark 458 Hill, London, United Kingdom SE5 8AF.

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Empirical Studies (Manuscript 2)

Sex differences in cognitive functioning of patients at-risk for psychosis and healthy controls – Results from the EU-GEI study

Stephanie Menghini-Müller, Erich Studerus, Sarah Ittig, Lucia R. Valmaggia, Matthew J. Kempton, Mark van der Gaag, Lieuwe de Haan, Barnaby Nelson, Rodrigo A. Bressan, Neus Barrantes-Vidal, Célia Jantac, Merete Nordentoft, Stephan Ruhrmann, Gabriele Sachs, Bart P. Rutten, Jim van Os, Anita Riecher-Rössler, EU-GEI High Risk Study Group

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Sex differences in cognitive functioning of patients at-risk for psychosis and healthy controls: Results from the European Gene–Environment Interactions study

Stephanie Menghini-Müller[1], Erich Studerus[2], Sarah Ittig[1], Lucia R. Valmaggia[3], Matthew J. Kempton[4], Mark van der Gaag[5,6], Lieuwe de Haan[7,8], Barnaby Nelson[9], Rodrigo A. Bressan[10], Neus Barrantes-Vidal[11], Célia Jantac[12], Merete Nordentoft[13,14], Stephan Ruhrmann[15], Garbiele Sachs[16], Bart P. Rutten[17], Jim van Os[18,19,20], Anita Riecher-Rössler[1*] and the EU-GEI High Risk Study Group[21]

[1]University of Basel, Department of Psychiatry, Basel, Switzerland; [2]Department of Psychology, Division of Personality and Developmental Psychology, University of Basel, Basel, Switzerland; [3]Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom; [4]Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom; [5]Faculty of Behavioural and Movement Sciences, Department of Clinical Psychology and EMGO+ Institute for Health Care Research, VU University, Amsterdam, The Netherlands; [6]Department of Psychosis Research, Parnassia Psychiatric Institute, The Hague, The Netherlands; [7]Department Early Psychosis, AMC, Academic Psychiatric Centre, Amsterdam, The Netherlands; [8]Mental Health Institute, Arkin, Amsterdam, The Netherlands, Amsterdam, The Netherlands; [9]Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia; [10]LiNC—Lab Interdisciplinar Neurociências Clínicas, Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo—UNIFESP, São Paulo, Brazil; [11]Departament de Psicologia Clínica I de la Salut (Universitat Autònoma de Barcelona), Fundació Sanitària Sant Pere Claver (Spain), Spanish Mental Health Research Network (CIBERSAM), Barcelona, Spain; [12]University Paris Descartes, Hôpital Sainte-Anne, C'JAAD, Service Hospitalo-Universitaire, Inserm U894, Institut de Psychiatrie (CNRS 3557), Paris, France; [13]Mental Health Center Copenhagen, Copenhagen, Denmark; [14]Institute for Clinical Medicine, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark; [15]Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany; [16]Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria; [17]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht, The Netherlands; [18]Department Psychiatry, Brain Centre Rudolf Magnus, Utrecht University Medical Centre, Utrecht, The Netherlands; [19]Department of Psychiatry and Psychology, School for Mental Health and Neuroscience (MHeNS), Maastricht University Medical Centre, Maastricht, The Netherlands; [20]King's College London, King's Health Partners Department of Psychosis Studies, Institute of Psychiatry, London, United Kingdom and [21]A full list of authors and affiliations appears in the Appendix.

Abstract

Background. Sex differences in cognitive functioning have long been recognized in schizophrenia patients and healthy controls (HC). However, few studies have focused on patients with an at-risk mental state (ARMS) for psychosis. Thus, the aim of the present study was to investigate sex differences in neurocognitive performance in ARMS patients compared with HC.

Methods. The data analyzed in this study were collected within the multicenter European Gene–Environment Interactions study (11 centers). A total of 343 ARMS patients (158 women) and 67 HC subjects (33 women) were included. All participants completed a comprehensive neurocognitive battery. Linear mixed effects models were used to explore whether sex differences in cognitive functioning were present in the total group (main effect of sex) and whether sex differences were different for HC and ARMS (interaction between sex and group).

Results. Women performed better in social cognition, speed of processing, and verbal learning than men regardless of whether they were ARMS or HC. However, only differences in speed of processing and verbal learning remained significant after correction for multiple testing. Additionally, ARMS patients displayed alterations in attention, current IQ, speed of processing, verbal learning, and working memory compared with HC.

Conclusions. Findings indicate that sex differences in cognitive functioning in ARMS are similar to those seen between healthy men and women. Thus, it appears that sex differences in cognitive performance may not be specific for ARMS, a finding resembling that in patients with schizophrenic psychoses.

Research Article

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Author for correspondence:
*Anita Riecher-Rössler
E-mail: anita.riecher@unibas.ch

EUROPEAN PSYCHIATRIC ASSOCIATION

Introduction

Sex differences in schizophrenia have been described in almost all features of the illness, including incidence, prevalence, age at onset, symptomatology, course, and in the response to treatment,

but only reliably established in age at onset and course [1]. Sex-related differences in the illness course might be at least partially mediated by sex-related differences in cognitive functioning [2]. Reduced cognitive performance is one of the core features of schizophrenia and an important predictor of outcome [3]. Several studies have shown neurocognitive deficits already in patients with a so-called at-risk mental state (ARMS) for psychosis [4]. Furthermore, it has been found that ARMS patients with later conversion to psychosis performed worse at baseline in tests measuring attention/vigilance, speed of processing, verbal and visual learning, and current and premorbid IQ compared with patients who did not convert [4]. Consequently, several studies have shown that the prediction of transition to psychosis can be improved by including neurocognitive performance measures into multivariable risk prediction models [4–8].

Cognitive performance is not only dependent on different stages of psychotic disorders, but also on sex. In healthy controls (HC), it is well established that women tend to perform better than men in tasks measuring verbal abilities ($d = 0.24$; for meta-analysis, see reference [9]), whereas men tend to outperform women on visual–spatial tasks ($d = 0.45$; for meta-analysis, see [9]) [10–12]. Most studies indicate that these differences are also maintained in patients with schizophrenic psychoses (for reviews, see references [1,2]). Specifically, many studies have shown that women diagnosed with schizophrenia have a better performance in verbal learning and memory [1,13,14]. The female advantage in verbal domains has also been found in patients with first-episode psychosis (FEP), while men showed a better performance in tests of reaction time, visual memory, and executive functions [1,10].

The impact of sex on cognitive functioning in ARMS has received considerable attention in the literature in recent years. A meta-regression analysis based on 19 studies assessing neuropsychological performance in 1,188 ARMS patients (women, $n = 523$; 44%) and 1,029 HC (women, $n = 464$; 45%) showed a trend-level significance effect of sex on cognitive performance, with females performing relatively better than males [15]. Our own group investigated sex differences in cognitive functioning in 118 ARMS patients (women, $n = 45$; 38%), 88 FEP patients (women, $n = 32$; 36%), and 86 HC (women, $n = 41$; 47%) [10]. Women performed better in the domain of verbal learning and memory whereas men showed a shorter reaction time during the working memory task across all groups. However, these differences did not withstand correction for multiple testing. Taken together, existing studies indicate that female patients with psychotic disorders or being at clinical high risk for psychosis do not perform better than males over and above what we see in HC.

To the best of our knowledge, the present study is the first to investigate sex differences in cognitive functioning in a large multinational sample of ARMS patients by using an extended neuropsychological battery and a healthy comparison group. The goal of the study was to elucidate whether sex differences in cognitive functioning differ between ARMS and HC subjects. Based on the evidence above and our own findings, we expected a better performance of women in the domain of verbal learning and memory irrespective of group.

Methods

Setting and recruitment

The neuropsychological data analyzed in this study were collected within the EUropean Gene–Environment Interactions (EU-GEI) study, which aims to identify the interactive genetic, clinical, and environmental determinants of schizophrenia [16]. EU-GEI is a naturalistic prospective multicenter study that consisted of a baseline and up to three follow-up time points (at 6 months, 12 months, and 24 months). Data were collected from May 1, 2010 to August 6, 2015. For the current analyses, only baseline data, that is, at intake into the study, were used.

ARMS participants were recruited from 11 Early Detection and Intervention Centers (London, Amsterdam, The Hague, Vienna, Basel, Cologne, Copenhagen, Paris, Barcelona, Melbourne, Saõ Paulo). They were referred to the EU-GEI study by primary health care services, mental health professionals, or themselves or their families.

Control participants were recruited by four of the above-mentioned centers: the Institute of Psychiatry, Psychology, and Neuroscience (IoPPN) in London, the Personal Assessment and Crisis Evaluation Clinic in Melbourne, and the Amsterdam Medical Center and Parnassia, The Hague. They were approached by telephone and through advertisements at educational institutes. In Melbourne, controls were additionally approached at community centers/noticeboards and advertised via online platforms. Controls were matched to the ARMS patients in terms of age, sex, migrant, and ethnic status. All participants were screened with an inclusion/exclusion checklist (see below).

The protocol of the EU-GEI study was approved by the institutional review boards of all study sites. EU-GEI was conducted in accordance with the Declaration of Helsinki. The Medical Ethics Committees of all participating sites approved the study protocol.

Inclusion and exclusion criteria

Inclusion criteria for ARMS patients were: aged 14–45 (most of them were between 18 and 35 years); being at-risk for psychosis as defined by the comprehensive assessment of at-risk mental state (CAARMS) [17]; adequate language skills corresponding to each center; and consent to study participation. The exclusion criteria were: prior experience of a psychotic episode of more than 1-week as determined by the CAARMS [17] and Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM Disorders (SCID)) [18]; previous treatment with an antipsychotic for a psychotic episode; and IQ < 60.

Inclusion criteria for controls were: aged 18–35; adequate language skills local to each center; no evidence of current or past psychosis (including treatment with antipsychotic medication). Exclusion criteria for controls were similar to those for ARMS participants. Additionally, controls were excluded if they met the criteria for an ARMS status as defined by the CAARMS [17].

Detection procedure

The CAARMS was used to identify ARMS patients [17]. The CAARMS is a semi-structured interview that encompasses psychotic symptoms and a range of other psychopathological symptoms present during the psychosis prodrome. Individuals were classified as being in an ARMS for psychosis if they met at least one of the following risk criteria: (i) attenuated psychotic symptoms (psychotic symptoms subthreshold either in intensity or frequency); (ii) brief limited psychotic symptoms (recent episode of brief psychotic symptoms that spontaneously resolved within 1 week); or (iii) vulnerability group (a first-degree relative with a psychotic disorder or a diagnosis of a schizotypal personality disorder in combination with a significant drop in functioning). The full criteria can be found elsewhere [17].

Assessment of sociodemographic and clinical characteristics

Sociodemographic characteristics (e.g. age, sex, ethnicity) were obtained using the modified Medical Research Council sociodemographic schedule [19]. Current cannabis frequency was assessed with the modified version of the Cannabis Experience Questionnaire [20]. Data on comorbid affective and anxiety disorders were assessed with the SCID [18]. Psychiatric medication (i.e., use of antipsychotics, antidepressants, and sedatives) was obtained using a medical history questionnaire, designed by the EU-GEI group. The general level of functioning was assessed with the modified version of the Global Assessment of Functioning (GAF) scale [21].

Classification and assessment of neuropsychology

Neuropsychological performance of each participant was assessed by trained psychiatrists, psychologists, and research assistants. The neuropsychological tests covered the following seven domains: attention/vigilance, reasoning/problem solving, speed of processing, verbal learning, working memory, social cognition, and current IQ. Test scores were assigned to cognitive domains in accordance with Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) [22]. Tests that are not part of the MCCB were assigned to domains according to their most commonly used function. The following measures were used to cover the cognitive domains of interest:

- Attention/vigilance: Digit Span Forward subtest of the Wechsler Adult Intelligence Scale-third edition (WAIS-III) [23];
- Reasoning/problem solving: Beads Task [24];
- Speed of processing: Digit Symbol Test of the WAIS-III and the Trail-Making Test parts A and B [25];
- Verbal Learning: Rey Auditory Verbal Learning Test [26];
- Working memory: Digit Span Backwards and Arithmetic subtests of the WAIS-III [23];
- Social cognition: Degraded Affect Recognition Task [27] and the Benton Facial Recognition Test [28]; and
- Current IQ: Block Design total raw score, the information total raw score and the estimate of the total IQ of the shortened WAIS-III [23,29].

Assessment of psychopathology

The Brief Psychiatric Rating Scale expanded version (BPRS-E) [30] was used to assess psychopathology. Sex differences were investigated using the BPRS total score and the following subscales: BPRS positive symptoms and BPRS negative symptoms [31].

Statistical analyses

All statistical analyses were performed using R [32]. Because observations were nonindependent, that is, observations from the same center were more similar than observations from different centers, sex differences were analyzed using linear mixed effects models including sex and group (ARMS, HC) as a fixed effects factors and randomly varying intercepts per center to account for the clustering in the data. Linear mixed effects models were applied to evaluate the main effects of sex and group (ARMS, HC) as well as their interactions on cognitive functioning. Dependent variables were *z*-transformed before inclusion to models and sex was included as a binary variable with 0 and 1 describing men and women, respectively. Thus, the regression coefficient for sex described the standardized mean difference (SMD) of women compared with men. The results are presented with and without correction for multiple testing. We used the false discovery rate procedure to adjust *p*-values for multiple testing [33].

Results

Sample description

The sample of the present study consisted of 343 ARMS patients (185 men, 158 women) and 67 HC subjects (34 men, 33 women). Sociodemographic and clinical characteristics of our sample are presented in Table 1. Cannabis use was more frequent in male ARMS patients than female ARMS patients (30.51% vs. 18.46% used cannabis at least a few times per year). With regard to comorbid affective and anxiety disorders, female ARMS patients showed more often a current anxiety disorder as well as posttraumatic stress disorders (PTSD) compared with male ARMS patients. There were no significant sex differences regarding any current affective disorder (i.e., current depressive, manic, or hypomanic episode and dysthymic disorder), neither for ARMS nor for HC. With regard to psychopathology, male ARMS patients showed significantly more severe BPRS "negative symptoms" ($p = 0.006$) than female ARMS patients. There were no sex differences in ARMS and HC with regard to age, years of education, current psychiatric medication, global functioning, BPRS "positive symptoms" and BPRS "total score."

Effects of sex and diagnostic group on cognitive functioning

Means and standard deviations (*SD*) of the total group, ARMS, and HC are presented in Table 2. Table 3 shows the results of the mixed effects models using neurocognitive performance as the continuous dependent variable and sex as well as group (ARMS, HC) as fixed effects factors. SMDs of the neuropsychological measures are additionally presented in Figure 1.

In the combined sample of ARMS and HC, women recognized more angry faces in the "Degraded Faces Affect Recognition" social cognition task ($p = 0.034$, $b = 0.25$), performed better in the "Digital Symbol Coding" speed of processing task ($p \leq 0.001$, $b = 0.44$) of the WAIS-III, and remembered more words in the "Rey Auditory Verbal Learning Test (RAVLT) delayed recall" ($p = 0.003$, $b = 0.41$) and "RAVLT trials 1 to 5" ($p = 0.001$, $b = 0.40$) than men. However, after correction for multiple testing, only the differences in "Digital Symbol Coding" and the RAVLT measures remained statistically significant.

Effects of diagnostic group are presented in Table 3. ARMS patients performed significantly worse in all cognitive performance scores, except in all scores of the problem solving and social cognition tasks.

There was one statistically significant interaction between sex and group (ARMS, HC) on the "WAIS-III Digit Span Backwards" working memory task ($p = 0.011$), which was due to a significantly better performance of female HC compared with male HC ($p < 0.026$, $b = -0.59$) and a nonsignificantly worse performance of female ARMS patients compared with male ARMS patients ($p = 0.186$, $b = 0.16$). However, this sex × group interaction was no longer significant after correction for multiple testing.

Table 1. Sociodemographic and clinical sample characteristics

	ARMS					HC				
	All	Men	Women	*p* value		All	Men	Women	*p* value	
	(*n* = 343)	(*n* = 185)	(*n* = 158)		*N*	(*n* = 67)	(*n* = 34)	(*n* = 33)		*N*
Age	22.4 (4.91)	22.7 (5.08)	22.1 (4.70)	0.210	343	22.9 (4.09)	23.0 (4.09)	22.7 (4.15)	0.720	67
Ethnicity				0.481	342				0.009**	67
White	245 (71.6%)	136 (73.5%)	109 (69.4%)			42 (62.7%)	23 (67.6%)	19 (57.6%)		
Black	34 (9.94%)	18 (9.73%)	16 (10.2%)			10 (14.9%)	8 (23.5%)	2 (6.06%)		
Mixed	28 (8.19%)	16 (8.65%)	12 (7.64%)			6 (8.96%)	0 (0.0%)	6 (18.2%)		
Asian	11 (3.22%)	6 (3.24%)	5 (3.18%)			9 (13.4%)	3 (8.82%)	6 (18.2%)		
North African	12 (3.51%)	6 (3.24%)	6 (3.82%)			0 (0.0%)	0 (0.0%)	0 (0.0%)		
Other	12 (3.51%)	3 (1.62%)	9 (5.73%)			0 (0.0%)	0 (0.0%)	0 (0.0%)		
Years of education	14.4 (3.07)	14.4 (3.28)	14.4 (2.83)	0.989	302	16.1 (2.79)	16.6 (2.97)	15.6 (2.55)	0.169	65
Cannabis current frequency				0.029*	334				0.081	67
None	247 (74.0%)	121 (68.4%)	126 (80.3%)			49 (73.1%)	22 (64.7%)	27 (81.8%)		
Only once or twice	4 (1.20%)	2 (1.13%)	2 (1.27%)			1 (1.49%)	0 (0.0%)	1 (3.03%)		
A few times each year	17 (5.09%)	7 (3.95%)	10 (6.37%)			4 (5.97%)	4 (11.8%)	0 (0.0%)		
A few times each month	17 (5.09%)	12 (6.78%)	5 (3.18%)			7 (10.4%)	4 (11.8%)	3 (9.09%)		
(More than) once a week	11 (3.29%)	9 (5.08%)	2 (1.27%)			3 (4.48%)	1 (2.94%)	2 (6.06%)		
Every day	38 (11.4%)	26 (14.7%)	12 (7.64%)			3 (4.48%)	3 (8.82%)	0 (0.0%)		
Antipsychotics currently	30 (11.8%)	15 (11.6%)	15 (11.9%)	1.000	255	0 (0.0%)	0 (0.0%)	0 (0.0%)		56
Antidepressants currently	82 (32.2%)	39 (30.2%)	43 (34.1%)	0.595	255	2 (3.57%)	0 (0.0%)	2 (7.14%)	0.491	56
Sedatives currently	15 (5.88%)	7 (5.43%)	8 (6.35%)	0.963	255	1 (1.79%)	0 (0.0%)	1 (3.57%)	1.000	56
Current affective disorder	127 (37.0%)	60 (32.4%)	67 (42.4%)	0.073	343	0 (0.0%)	0 (0.0%)	0 (0.0%)		67
Current anxiety disorder	166 (48.4%)	73 (39.5%)	93 (58.9%)	0.001**	343	5 (7.46%)	2 (5.88%)	3 (9.09%)	0.673	67
Current OCD	29 (9.70%)	16 (10.1%)	13 (9.29%)	0.975	299	0 (0.0%)	0 (0.0%)	0 (0.0%)		53
Current PTSD	34 (10.6%)	11 (6.40%)	23 (15.4%)	0.015*	321	0 (0.0%)	0 (0.0%)	0 (0.0%)		65
GAF disability, impairment	55.5 (12.3)	55.8 (12.4)	55.1 (12.1)	0.584	331	85.0 (8.98)	85.2 (8.15)	84.7 (9.92)	0.819	66
BPRS positive symptoms	7.48 (3.17)	7.67 (3.28)	7.27 (3.03)	0.254	323	3.17 (0.53)	3.13 (0.43)	3.21 (0.63)	0.550	59
BPRS negative symptoms	5.05 (2.40)	5.38 (2.65)	4.66 (2.02)	0.006**	324	3.00 (0.00)	3.00 (0.00)	3.00 (0.00)	0.325	59
BPRS total score	43.6 (10.2)	44.1 (10.6)	43.0 (9.67)	0.361	324	25.4 (2.61)	25.3 (2.24)	25.6 (3.01)	0.618	59

Abbreviations: ARMS, at-risk mental state; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; HC, healthy controls; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder.
Continuous variables are described by means and standard deviation in brackets.
*$p < 0.05$.
**$p < 0.01$.

The results did not change, when age or frequent cannabis use (i.e., at least several times per week) were included as covariates.

Discussion

To the best of our knowledge, this is the first study investigating sex-related neurocognitive performance differences in a multinational ARMS sample of this size, using a comprehensive neuropsychological battery and a healthy comparison group. In line with our hypotheses, women showed superior performance in the domain of verbal learning and memory independent of whether they were ARMS patients or HC. Furthermore, women outperformed men on measures of speed of processing (i.e., Digital Symbol Coding total raw score) and social cognition (i.e., Degraded Facial Affect Recognition Task (DFAR) angry faces total correct), whereas men outperformed women on a trend-wise level on a task of working memory (i.e., arithmetic total raw score). Additionally, our results show that ARMS patients displayed alterations in attention, current IQ, speed of processing, verbal learning, and working memory compared with HC. However, we will not discuss this aspect any further since it is not the focal point of the present study.

Finally, we found a sex × group interaction effect on working memory (i.e., WAIS-III Digit Span Backwards), which was due to a significantly better performance of female HC compared with male HC and a nonsignificantly better performance of male ARMS patients compared with female ARMS patients. However,

Table 2. Means and standard deviations of neuropsychological test data in ARMS patients and HC

	Total group			ARMS			HC		
	All	Men	Women	All	Men	Women	All	Men	Women
	(*n* = 410)	(*n* = 219)	(*n* = 191)	(*n* = 343)	(*n* = 185)	(*n* = 158)	(*n* = 67)	(*n* = 34)	(*n* = 33)
Attention									
WAIS-III Digit Span Forward	9.69 (2.26)	9.66 (2.19)	9.73 (2.34)	9.51 (2.20)	9.50 (2.16)	9.51 (2.24)	10.7 (2.35)	10.5 (2.18)	11.0 (2.57)
Current IQ									
Block Design total raw score	43.8 (15.2)	44.8 (15.2)	42.7 (15.3)	42.7 (15.5)	43.8 (15.1)	41.4 (15.8)	49.3 (12.9)	49.7 (14.8)	48.9 (11.0)
Estimate of total IQ	101 (17.9)	102 (18.7)	100 (17.0)	98.6 (16.8)	99.9 (17.6)	97.2 (15.9)	113 (18.1)	112 (20.5)	113 (15.7)
Information total raw score	16.9 (6.56)	17.5 (6.56)	16.2 (6.51)	16.3 (6.73)	17.1 (6.71)	15.5 (6.68)	19.4 (4.98)	19.4 (5.47)	19.4 (4.52)
Problem solving									
Beads task draws to decision	6.62 (4.63)	6.90 (5.06)	6.31 (4.11)	6.54 (4.70)	6.74 (5.20)	6.33 (4.09)	7.02 (4.29)	7.73 (4.21)	6.22 (4.32)
Social cognition									
BFR total correct	22.3 (2.33)	22.3 (2.24)	22.3 (2.43)	22.2 (2.32)	22.3 (2.24)	22.2 (2.42)	22.6 (2.36)	22.1 (2.31)	23.1 (2.36)
DFAR angry faces total correct	10.2 (4.90)	9.67 (4.90)	10.7 (4.84)	10.5 (4.71)	9.99 (4.79)	11.0 (4.58)	8.61 (5.53)	7.94 (5.23)	9.30 (5.82)
DFAR frightened faces total correct	8.59 (4.25)	8.17 (4.21)	9.07 (4.26)	8.80 (4.09)	8.26 (4.09)	9.43 (4.02)	7.50 (4.89)	7.68 (4.85)	7.31 (5.01)
DFAR happy faces total correct	12.8 (5.08)	12.5 (5.23)	13.1 (4.89)	13.1 (4.78)	12.7 (5.07)	13.5 (4.38)	11.3 (6.23)	11.4 (6.01)	11.1 (6.54)
DFAR neutral faces total correct	11.4 (4.84)	11.1 (4.95)	11.6 (4.72)	11.6 (4.57)	11.3 (4.76)	12.0 (4.31)	10.2 (5.97)	10.6 (5.92)	9.81 (6.09)
Speed of processing									
Digital Symbol Coding total raw score	73.1 (16.1)	70.2 (16.6)	76.4 (15.0)	71.7 (15.8)	69.2 (16.6)	74.5 (14.4)	80.1 (15.9)	75.2 (15.9)	85.0 (14.6)
TMT-A time to completion	29.6 (12.3)	30.7 (13.9)	28.4 (10.1)	30.2 (12.2)	31.2 (13.6)	29.1 (10.3)	26.6 (12.8)	28.1 (15.6)	25.0 (8.62)
TMT-B time to completion	70.3 (29.4)	74.6 (30.8)	65.7 (27.2)	73.2 (30.4)	77.9 (31.6)	68.0 (28.2)	56.3 (18.8)	58.0 (19.5)	54.4 (18.2)
Verbal learning									
RAVLT delayed recall correct	10.7 (3.14)	10.2 (3.31)	11.4 (2.79)	10.6 (3.05)	10.0 (3.21)	11.2 (2.72)	11.4 (3.48)	10.9 (3.76)	12.0 (3.09)
RAVLT trial 1 correct	6.82 (2.02)	6.58 (1.93)	7.09 (2.09)	6.69 (1.99)	6.45 (1.86)	6.98 (2.11)	7.43 (2.04)	7.25 (2.14)	7.64 (1.93)
RAVLT trials 1–5 correct	52.2 (9.91)	50.6 (9.68)	54.0 (9.88)	51.3 (9.98)	49.9 (9.64)	53.1 (10.1)	56.3 (8.50)	54.1 (9.20)	58.7 (7.01)
Working memory									
Arithmetic total raw score	13.5 (4.76)	14.1 (4.68)	12.8 (4.76)	13.1 (4.70)	13.8 (4.64)	12.3 (4.65)	15.5 (4.58)	15.9 (4.60)	15.1 (4.60)
WAIS-III Digit Span Backwards	6.73 (2.27)	6.74 (2.28)	6.71 (2.27)	6.60 (2.19)	6.72 (2.30)	6.46 (2.06)	7.44 (2.58)	6.87 (2.21)	8.17 (2.87)

Abbreviations: ARMS, at-risk mental state; BFR, Benton Facial Recognition Test; DFAR, Degraded Facial Affect Recognition Task; HC, healthy controls; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale.

only sex differences in the total group in speed of processing and verbal learning remained significant after correction for multiple testing.

With regard to verbal learning and memory, our finding that the female advantage is equally present in ARMS patients as in HC is in line with previous research [1,15]. Furthermore, it corroborates the findings of an earlier study of our own group that reported no interaction effect between diagnostic group (i.e., ARMS, FEP, HC) and verbal learning and memory [10].

Regarding processing speed, our finding that women perform better than men is also consistent with earlier findings from the general population [34,35] and patients with schizophrenia [36,37]. To the best of our knowledge, this is the first study examining sex differences in ARMS and healthy subjects by using well-established tests to evaluate processing speed (i.e., Trail Making Test, WAIS-III Digit Symbol subtest). A previous study has investigated sex-related cognitive performance differences in ARMS, FEP and HC but did not include tests specifically measuring processing speed [10]. However, the authors found a shorter reaction time for men in the working memory task independent of diagnostic group. They explain the findings by a superior working memory performance rather than generally enhanced processing speed in men as no sex differences in reaction time during the Continuous Performance Test and the Go/No-Go subtest of the Test of Attentional Performance (TAP) were detected, while maintaining a comparable overall working memory performance level [10].

Table 3. *p* values and coefficients of fixed effects of mixed effects models

	Group			Sex			Group × sex		
	p value	*p* value corr[a]	Coef	*p* value	*p* value corr[a]	Coef	*p* value	*p* value corr[a]	Coef
Attention									
WAIS-III Digit Span Forward	<0.001***	0.002**	0.55	0.441	0.530	0.11	0.467	0.782	0.22
Current IQ									
Block Design total raw score	<0.001***	<0.001***	0.59	0.364	0.505	−0.12	0.561	0.782	0.15
Estimate of total IQ	<0.001***	<0.001***	0.88	0.658	0.697	−0.06	0.385	0.782	0.22
Information total raw score	<0.001***	<0.001***	0.61	0.329	0.493	−0.13	0.277	0.774	0.29
Problem solving									
Beads task draws to decision	0.331	0.426	0.15	0.098	0.252	−0.23	0.659	0.782	−0.13
Social cognition									
BFR total correct	0.143	0.198	0.22	0.201	0.329	0.18	0.124	0.705	0.45
DFAR angry faces total correct	0.435	0.489	−0.10	0.034*	0.151	0.25	0.695	0.782	0.09
DFAR frightened faces total correct	0.421	0.489	−0.11	0.409	0.525	0.10	0.112	0.705	−0.40
DFAR happy faces total correct	0.531	0.563	−0.08	0.547	0.615	0.07	0.301	0.774	−0.24
DFAR neutral faces total correct	0.922	0.922	−0.01	0.922	0.922	0.01	0.266	0.774	−0.27
Speed of processing									
Digital Symbol Coding total raw score	<0.001***	<0.001***	0.63	<0.001***	0.011*	0.44	0.157	0.705	0.37
TMT-A time to completion	0.017*	0.028*	−0.36	0.162	0.291	−0.20	0.549	0.782	−0.17
TMT-B time to completion	<0.001***	<0.001***	−0.65	0.122	0.261	−0.21	0.641	0.782	0.13
Verbal learning									
RAVLT delayed recall correct	0.026*	0.040*	0.33	0.003**	0.019*	0.41	0.936	0.936	−0.02
RAVLT trial 1 correct	0.016*	0.028*	0.34	0.069	0.206	0.24	0.874	0.926	−0.04
RAVLT trials 1–5 correct	<0.001***	<0.001***	0.49	0.001**	0.011*	0.40	0.593	0.782	0.13
Working memory									
Arithmetic total raw score	<0.001***	<0.001***	0.60	0.064	0.206	−0.24	0.580	0.782	0.14
WAIS-III Digit Span Backwards	<0.001***	0.002**	0.51	0.130	0.261	0.22	0.011*	0.197	0.75

Abbreviations: BFR, Benton Facial Recognition Test; coef, *y*-standardized regression coefficients of fixed effects; DFAR, Degraded Facial Affect Recognition Task; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale.
[a]Corrected for multiple testing using Benjamini–Hochberg method.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

A strength of our study is that we examined sex differences with well-established tests using the classification of the MATRICS panel [22,38]. As the MCCB domains are well known in schizophrenia research, this may help future studies to compare sex-related cognitive performance differences in ARMS and schizophrenic patients. Furthermore, this is the first study to investigate sex differences in cognitive functioning in an ARMS sample of this size.

However, there are some limitations to the present study that need to be acknowledged. Our neuropsychological test battery was originally selected to identify genetic and environmental interactions in psychosis and not specifically to detect sex differences. Accordingly, the test battery did not include other sensitive tasks to detect sex differences such as visuo-spatial tasks. Additionally, the domain of visual learning in the MATRICS consensus battery was not covered. Furthermore, our control group was rather small in comparison to the ARMS group, which reduced the statistical power to detect interaction effects between sex and group. Finally, it is important to note that sex-related cognitive performance differences depend on a wide variety of conditions, for example, the severity of symptoms and especially the fluctuation of estrogen levels during the menstrual cycle in women (for review, see reference [1]). There is evidence that high levels of estrogen at the mid-luteal point are associated with better verbal memory and diminished spatial ability [39]. Thus, it is possible that some effects would have changed if we had measured women at a specific time point during their monthly cycle. Unfortunately, in our study no assessment of the time point during the monthly cycle was performed.

Taken together, our findings indicate that sex differences in cognitive functioning in ARMS patients are very similar to those seen in the general population and in schizophrenia patients.

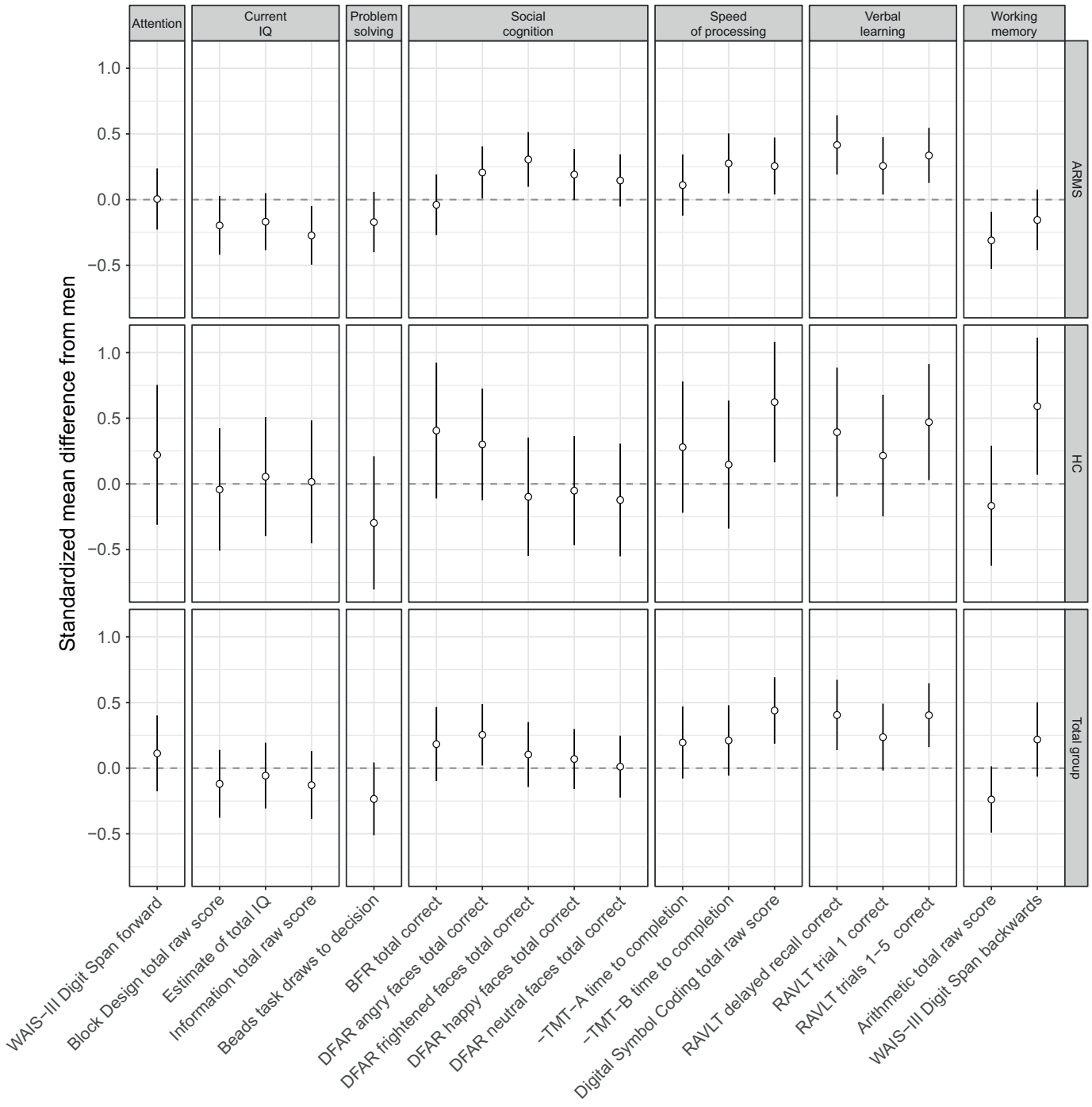

Figure 1. Cognitive performance of women compared with men in at-risk mental state for psychosis individuals and healthy controls. The dotted horizontal line at zero represents the performance of men. Differences are expressed in units of standard deviation and are significant if the 95% confidence interval (vertical line) does not overlap with zero. Variables with a minus sign were reversed so that positive scores always represent good performance. Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale.

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Conflict of Interest. All authors declare not to have any conflicts of interest that might be interpreted as influencing the content of the manuscript.

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Appendix

EU-GEI High Risk Study Group—Author List

Philip McGuire[2], Lucia R. Valmaggia[3], Matthew J. Kempton[2], Maria Calem[2], Stefania Tognin[2], Gemma Modinos[2], Lieuwe de Haan[4,7], Mark van der Gaag[8,10], Eva Velthorst[5,11], Tamar C. Kraan[6], Daniella S. van Dam[4], Nadine Burger[7], Barnaby Nelson[12,13], Patrick McGorry[12,13], G. Paul Amminger[12,13], Christos Pantelis[14], Athena Politis[12,13], Joanne Goodall[12,13], Anita Riecher-Rössler[1], Stefan Borgwardt[1], Charlotte Rapp[1], Sarah Ittig[1], Erich Studerus[1], Renata Smieskova[1], Rodrigo Bressan[15], Ary Gadelha[15], Elisa Brietzke[16], Graccielle Asevedo[15], Elson Asevedo[15], Andre Zugman[15], Neus Barrantes-Vidal[17], Tecelli Domínguez-Martínez[18], Anna Racioppi[19], Lídia Hinojosa-Marqués[19], Thomas R. Kwapil[20], Manel Monsonet[19], Mathilde Kazes[21], Claire Daban[21], Julie Bourgin[21], Olivier Gay[21],

Célia Mam-Lam-Fook[21], Marie-Odile Krebs[21], Dorte Nordholm[22], Lasse Randers[22], Kristine Krakauer[22], Louise Glenthøj[22], Birte Glenthøj[23], Merete Nordentoft[22], Stephan Ruhrmann[24], Dominika Gebhard[24], Julia Arnhold[25], Joachim Klosterkötter[24], Gabriele Sachs[26], Iris Lasser[26], Bernadette Winklbaur[26], Philippe A. Delespaul[27,28], Bart P. Rutten[29], and Jim van Os[29,30].

Affiliations

[1]University Psychiatric Hospital, CH-4002 Basel, Switzerland; [2]Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, United Kingdom; [3]Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, United Kingdom; [4]Amsterdam UMC, University of Amsterdam, Psychiatry, Department Early Psychosis, Amsterdam, The Netherlands; [5]Department of Psychiatry and Seaver Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York, USA; [6]Mental Health Institute Arkin, Amsterdam, The Netherlands; [7]Arkin Amsterdam; [8]VU University, Faculty of Behavioral and Movement Sciences, Department of Clinical Psychology and Amsterdam Public Mental Health Research Institute, 1081 BT Amsterdam, The Netherlands; [9]Mental Health Institute Noord-Holland Noord, Hoorn, The Netherlands; [10]Parnassia Psychiatric Institute, Department of Psychosis Research, 2512 HN The Hague, The Netherlands; [11]Early Psychosis Section, Department of Psychiatry, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; [12]Orygen, The National Centre of Excellence in Youth Mental Health, University of Melbourne, Melbourne, Australia; [13]Centre for Youth Mental Health, University of Melbourne, Parkville, Victoria 485 3052, Australia; [14]Melbourne Neuropsychiatry Centre, The University of Melbourne, Melbourne, Australia; [15]LiNC—Lab Interdisciplinar Neurociências Clínicas, Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo—UNIFESP, São Paulo, Brazil; [16]Depto Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo—UNIFESP, São Paulo, Brazil; [17]Departament de Psicologia Clínica i de la Salut (Universitat Autònoma de Barcelona), Fundació Sanitària Sant Pere Claver (Spain), Spanish Mental Health Research Network (CIBERSAM), Spain; [18]CONACYT-Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Mexico; [19]Departament de Psicologia Clínica i de la Salut (Universitat Autònoma de Barcelona), Bellaterra, Spain; [20]Department of Psychology, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA; [21]University Paris Descartes, GHU Paris Sainte-Anne, C'JAAD, Service Hospitalo-Universitaire, Inserm 1266, Institut de Psychiatrie (CNRS 3557) Paris, France; [22]Mental Health Center Copenhagen and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, Mental Health Center Glostrup, Mental Health Services in the Capital Region of Copenhagen, University of Copenhagen, Copenhagen, Denmark; [23]Centre for Neuropsychiatric Schizophrenia Research (CNSR) & Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark; [24]Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany; [25]Psyberlin, Berlin, Germany; [26]Medical University of Vienna, Department of Psychiatry and Psychotherapy, Vienna, Austria; [27]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, 6200 MD 464 Maastricht, The Netherlands; [28]Mondriaan Mental Health Trust, 4436 CX Heerlen, The Netherlands; [29]Medical University of Vienna, Department of Psychiatry and Psychotherapy; [30]Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, United Kingdom.

Empirical Studies (Manuscript 3, co-authorship)

Gender differences in first-self perceived signs and symptoms in patients with an at-risk mental state and first-episode psychosis

Ulrike Heitz, Erich Studerus, Stephanie Menghini-Müller, Martina Papmeyer, Laura Egloff, Sarah Ittig, Astrid Navarra, Christina Andreou, Anita Riecher-Rössler

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ORIGINAL ARTICLE

Gender differences in first self-perceived signs and symptoms in patients with an at-risk mental state and first-episode psychosis

Ulrike Heitz[1] | Erich Studerus[1] | Stephanie Menghini-Müller[1] | Martina Papmeyer[2] | Laura Egloff[1] | Sarah Ittig[1] | Astrid Navarra[1] | Christina Andreou[1] | Anita Riecher-Rössler[1]

[1]Center for Gender Research and Early Detection, University of Basel Psychiatric Hospital, Basel, Switzerland

[2]Rehabilitation Services and Care Unit, Swiss Paraplegic Research, Guido A. Zäch Strasse 4, 6207 Nottwil, Switzerland

Correspondence
A. Riecher-Rössler. Center for Gender Research and Early Detection. University of Basel Psychiatric Hospital Wilhelm Klein-Str. 27, CH-4002, Basel. Switzerland.
Email: anita.riecher@upkbs.ch

Aim: Gender differences in the current symptomatology of patients with psychotic disorders have previously been described in the literature. However, it has not yet been investigated whether gender differences exist in the very first self-perceived signs or symptoms of illness onset. The aim of this study was to investigate this aspect in at-risk mental state (ARMS) and first-episode psychosis (FEP) patients.

Methods: ARMS and FEP were recruited via the early detection of psychosis (FePsy) clinic Basel, Switzerland. The Basel Interview for Psychosis (BIP) was used to retrospectively assess the first 3 self-perceived signs and symptoms at illness onset. Differences between gender and patient groups on single item and symptom cluster levels were analysed using logistic regression models.

Results: One-hundred-thirty six ARMS (91 men, 45 women) and 89 FEP patients (63 men, 26 women) could be recruited for this study. On a single item level, women more frequently reported "unusual anxiety, fears" and men (at a trend level) "social withdrawal" as being among their 3 first self-perceived symptoms, independent of diagnostic group. On the symptom cluster level, women more frequently reported "increased worrying/anxiety" and (sub-threshold) "hallucinations", independent of diagnostic group. Problems with "thinking, concentration" were reported more frequently by men in the ARMS group only.

Conclusion: Our results suggest that only few and relatively small gender differences exist in the first self-perceived signs and symptoms. While men initially mainly notice negative/cognitive symptoms, women first notice (sub-threshold) positive and affective symptoms.

KEYWORDS

BIP, gender, prodromal, psychopathology, psychotic disorder

1 | INTRODUCTION

Gender differences in schizophrenic psychoses have long been reported and debated. Among the most replicated findings are differences in age of onset, which is earlier in men, while women have a second peak of illness onset around menopause (Eranti, MacCabe, Bundy, & Murray, 2013; Häfner, Maurer, Löffler, & Riecher-Rössler, 1993; Häfner, Riecher-Rössler, Fätkenheuer et al., 1991; Häfner, Riecher-Rössler, Maurer et al., 1991)—a pattern suggested to be due to the protective effects of high oestrogen levels in women before menopause (Häfner, Riecher-Rössler, Maurer et al., 1991; Häfner, Riecher-Rössler et al., 1993; Riecher-Rössler, 2017). Additionally, recent reviews indicate a slightly increased incidence of schizophrenic psychoses in men compared to women (van der Werf et al., 2014). Moreover, men have been found to abuse substances more frequently and to have less illness insight, worse treatment adherence and poorer functional and social outcome (Abel, Drake, & Goldstein, 2010; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). Gender differences have also been reported with respect to symptomatology, although results in this area are inconsistent: While some studies

point towards more negative and cognitive symptoms in men and more affective and positive psychotic symptoms in women (for an overview see for example Waford et al., 2015), other studies either could not confirm any gender differences (Barajas, Banos, & Ochoa, 2007; Bertani et al., 2012; Häfner, Riecher-Rössler, Fätkenheuer et al., 1991) or found only few differences regarding illness behaviour (Häfner, Riecher-Rössler, Fätkenheuer et al., 1991; Häfner, Riecher-Rössler, Maurer et al., 1991).

In patients with an at-risk mental state (ARMS) for developing a psychotic disorder, few studies have looked into potential gender differences in current symptomatology. A recent review by Barajas, Ochoa, Obiols, and Lalucat-Jo (2015) concluded that gender differences are at the most modest, the most replicated finding being more negative symptoms in men. However, this conclusion was based on just 4 original studies investigating gender differences regarding psychopathology published up to that point (Cocchi et al., 2014; Corcoran et al., 2011; Lemos-Giraldez et al., 2009; Willhite et al., 2008). Since then, further studies have been published. A study by our own group (Gonzalez-Rodriguez et al., 2014) in ARMS and first-episode psychosis (FEP) patients revealed more positive psychotic symptoms in women (n = 43; total sample n = 117) and more negative symptoms in men, which, however, did not withstand correction for multiple testing. Similar small gender differences were reported in three further ARMS studies-more negative symptoms in men (men n = 159, total sample n = 239; Rietschel et al., 2015), more unusual experiences in women (women n = 148, total sample n = 356; Waford et al., 2015) and more depressive symptoms in women (women n = 53, total sample n = 129; Pruessner et al., 2017). However, these studies did not correct for multiple testing. On the other hand, a recent study by Kotlicka-Antczak et al. (2016) in a Polish ARMS sample did not find any gender differences in symptoms (total sample n = 99, men n = 45). The inconsistent findings of previous studies might furthermore be due to methodological differences between the studies, as pointed out in a previous paper (Gonzalez-Rodriguez et al., 2014). Thus, study samples are sometimes quite selective and not representing *all* men and women with emerging illness of a defined catchment area. As some studies only had small sample sizes, their statistical power might have been too low to detect gender differences, which probably are of only small or moderate effect size. Furthermore, the instruments used to assess the risk status and the symptomatology, correction for multiple testing and adjustment for confounders varied between the studies, making it difficult to directly compare the findings.

To extend the existing literature regarding gender differences in symptoms of ARMS and FEP individuals, it might be interesting to investigate what symptoms the patients in question notice themselves at the onset of the change in their psychological well-being. These individually experienced changes will subsequently be referred to as "first self-perceived symptoms." Although several studies have investigated current clinical symptoms in ARMS and FEP patients, only few have retrospectively assessed the very first self-perceived symptoms at illness onset (i.e., when the first decline in functioning or well-being was noted by the patient), which has been estimated to occur on average 4-5 years before first contact with psychiatry (Riecher-Rössler et al., 2006). Among the first was the ABC study (Häfner, Maurer et al., 1993; Häfner, Riecher-Rössler et al., 1993), which found that female FEP patients most frequently reported restlessness, depression and worrying as their initial symptoms, while men most frequently reported trouble with thinking and concentration and anxiety when interviewed retrospectively with the instrument for the retrospective assessment of the onset of schizophrenia (IRAOS). Iyer et al. (2008) retrospectively also assessed first self-perceived symptoms in FEP patients (using the Circumstances of Onset and Relapse Schedule) and found symptoms of depression and anxiety to be the most frequent signs. However, the authors did not report gender-specific early symptoms. An earlier publication of our own group (Aston et al., 2012) compared first self-perceived symptoms independent of gender in ARMS, FEP and depressive disorder patients and found "loss of energy" and "difficulties concentrating" to be the most frequent first self-perceived symptoms in the ARMS group, while FEP patients reported "depression" and "irritability" as first self-perceived symptoms. Furthermore, there was a considerable overlap of the first self-perceived symptoms between the three groups.

To the best of our knowledge, no study has yet investigated gender differences in first self-perceived symptoms in both ARMS and FEP patients. Such investigations could improve not only our understanding of the aetiopathology of psychotic disorders but also their early detection and treatment (Riecher-Rössler & Häfner, 2000; Seeman, 2013), which has become a major goal in psychiatry during the last 2 decades (Riecher-Rössler & McGorry, 2016).

Thus, the aim of the present study was to contribute to this field of research by investigating whether there are gender differences in the very first self-perceived symptoms in male and female ARMS and FEP patients. Based on the above-described literature, we hypothesized that overall only small gender differences would be observable in the first self-perceived symptoms of ARMS and FEP patients.

2 | METHODS

2.1 | Recruitment and screening procedure

ARMS and FEP patients were recruited for this study from March 2000 to March 2016 via the FePsy (Früherkennung für Psychosen; English: early detection of psychosis) clinic of the University of Basel Psychiatric Hospital, Switzerland. A detailed description of the FePsy study procedure can be found elsewhere (Haller et al., 2009; Riecher-Rössler et al., 2007). ARMS patients were identified using the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008), which is based on the PACE criteria (Yung et al., 1998) with one additional inclusion category. Inclusion as ARMS patient required one or more of the following: (1) "attenuated" psychotic symptoms, (2) brief limited intermittent psychotic symptoms (BLIPS), (3) a first degree relative with a psychotic disorder plus at least two risk factors or (4) combination of unspecific risk factors according to the BSIP (Riecher-Rössler et al., 2008). For inclusion, FEP patients had to fulfil the transition criteria for psychosis according to Yung et al. (1998), which were also assessed with the BSIP.

The following exclusion criteria were applied: age below 18 years, insufficient knowledge of German, IQ < 70, previous episode of schizophrenic psychosis (treated with antipsychotics above a

chlorpromazine equivalent of 2500 mg), psychosis clearly due to organic reasons or substance abuse, or psychotic symptomatology within a clearly diagnosed affective psychosis or borderline personality disorder (Riecher-Rössler et al., 2007).

All patients gave written informed consent. The Ethics Committee northwest/central Switzerland (EKNZ) approved the present study.

2.2 | Assessment of first signs and symptoms and duration of illness

The first signs and symptoms at illness onset as well as the duration of illness (DUI) were assessed with the Basel Interview for Psychosis (BIP; Riecher-Rössler et al., 2015). The BIP is a semi-structured interview specifically developed to assess risk factors and indicators of emerging psychosis as well as the temporal development of psychiatric symptoms over the whole lifespan in ARMS and FEP patients. A more detailed description of the BIP including its psychometric properties was described in a previous publication of our group (Riecher-Rössler et al., 2015). The BIP contains the following 6 sections: (1) social and physical development and family, (2) signs and symptoms, (3) vulnerability, (4) help-seeking behaviour, (5) illness insight and (6) evaluation of the interview. In the item 2.2.2 of section 2, patients are asked to openly name the first three symptoms they noticed when they first experienced a drop in well-being or functioning. Only patients who could spontaneously recall at least one first self-perceived change were included in the present study.

Each of the reported symptoms was subsequently categorized by the rater to 1 of 62 pre-defined single symptoms and one of the following 14 symptom clusters: (1) Worries, agitation, anxiety; (2) Physical complaints; (3) Thinking, concentration; (4) Compulsions; (5) Mood, emotions; (6) Sensitivity, suspiciousness; (7) Social isolation, behavioural changes; (8) Supernatural, inexplicable experiences; (9) Derealisation, depersonalization; (10) Hallucinations; (11) Delusions; (12) Thought insertion, broadcasting and withdrawal; (13) Feeling controlled by outside forces and (14) Problems with social adjustment.

It should be noted that the clusters concerning hallucinations and delusions capture sub-threshold as well as full-blown psychotic symptoms.

DUI was determined with the BIP by assessing the date of the first self-perceived sign or symptom and the date of first contact with our early detection service, and by subsequently calculating the time difference in months.

In addition, the Brief Psychiatric Rating Scale, Expanded version (BPRS-E; Lukoff, KH, & Ventura, 1986; Ventura, Nuechterlein, Liberman, Green, & Shaner, 1993) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1989) were used to obtain observer-based ratings of current symptomatology.

In the FePsy study, each patient is taken care of by a case-manager (CM) who is either a psychologist or psychiatrist. All assessments are organized by the responsible CM and all clinical interviews are carried out by the CM. The following clinical interviews are part of the FePsy study (in order of conduct): BSIP, structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-V) (SCID) and BIP. To assure a proper conduct of the interview, all CMs get an extensive training prior to their first assessment. Furthermore, all CMs take part in monthly psychopathology trainings including regularly the BIP. All trainings (pre-assessment trainings and monthly psychopathology trainings) are led by an experienced clinical psychologist or the head psychiatrist.

2.3 | Statistical analyses

The socio-demographic variables (i.e., age and years of education) as well as clinical characteristics (i.e., DUI, BPRS positive symptoms according to the factor analysis of Velligan et al., 2005, SANS total score) were compared between women and men in the ARMS, FEP and total groups using *t*-tests, except for the comparison of duration of untreated illness, where analyses were conducted using non-parametric Mann-Whitney U test, due to its non-normal properties.

The most frequently reported first self-perceived symptoms were listed on a single-item level. Logistic regression was used to compare the most commonly reported single items in the total sample, with presence of symptom (1 = yes/0 = no) as dependent variable and gender and group as independent variables.

Due to their great number, the single items were subsequently summarized on a cluster level in order to achieve more power in the analysis and to facilitate the interpretation of the results. Differences regarding the self-perceived symptoms on a cluster level were also analysed in the total group using logistic regression, with presence of symptom cluster (1 = presence of at least 1 symptom of the cluster/0 = otherwise) as dependent variable and gender and group as independent variables. In case of a significant interaction between gender and group, gender differences were analysed separately for ARMS and FEP patients. Complete case analysis was used to deal with missing values.

All data were analysed using the R environment for statistical computing (R Core Team, 2016). The level of significance was set at .05.

3 | RESULTS

3.1 | Socio-demographic and clinical characteristics

During the recruitment period, 181 ARMS and 132 FEP patients were recruited for the FePsy study. Of these, 136 ARMS (91 men, 45 women) and 89 FEP patients (63 men, 26 women) had completed the BIP items regarding first self-perceived symptoms and thus were included into this study. Excluded patients were not statistically different from included patients with regard to socio-demographic characteristics. Socio-demographic and clinical characteristics of the final sample are presented in Table 1. FEP patients were significantly older than ARMS patients. However, age did not differ between men and women, and there were no gender differences in years of education and DUI.

In the total sample, men scored significantly higher on the SANS total score than women. However, when ARMS and FEP patients were analysed separately, this difference was not significant.

TABLE 1 Socio-demographic and clinical characteristics

	All				ARMS				FEP			
	Women	Men			Women	Men			Women	Men		
	N = 71	*N* = 154	*P* value	*N*	*N* = 45	*N* = 91	*P* value	*N*	*N* = 26	*N* = 63	*P* value	*N*
Age	28.3 (9.59)	26.3 (6.41)	0.102	225	26.5 (9.20)	25.3 (6.06)	0.400	136	31.4 (9.62)	27.7 (6.65)	0.081	89
Years of education	11.9 (3.10)	11.3 (2.76)	0.189	225	11.5 (2.83)	11.3 (2.60)	0.624	136	12.5 (3.48)	11.4 (3.00)	0.153	89
Duration of untreated illness [months][a]	36.0 (76.1)	33.4 (61.7)	0.986	211	38.0 (72.0)	34.0 (60.0)	0.506	128	12.0 (55.3)	29.0 (68.0)	0.402	83
SANS total score	19.3 (15.7)	25.5 (17.0)	0.010*	218	18.6 (15.5)	24.4 (17.3)	0.056	133	20.6 (16.2)	27.2 (16.7)	0.105	85
BPRS positive symptoms	10.3 (4.34)	8.98 (4.44)	0.036*	218	7.84 (2.44)	6.42 (2.21)	0.002*	132	14.4 (3.58)	12.8 (4.20)	0.065	86

Values are given in means; standard deviation in parentheses.

ARMS = at-risk mental state; FEP = first-episode psychosis.

[a] Values are given in median; interquartile range in parentheses.

*Significant at $P < .05$.

Women had significantly higher scores in the BPRS Positive Symptoms Scale than men, in the total sample as well as in the ARMS subgroup.

3.2 | Most common first self-perceived symptoms: Single-item level

The five most frequently reported first self-perceived signs and symptoms in male and female ARMS and FEP patients are listed in Table 2.

Logistic regression models for each of the five most commonly reported symptoms revealed a significant main effect of gender in the absence of a significant group x gender interaction for the symptom "Unusual anxiety, fears" ($P = .016$; OR = 0.361 [0.154; 0.830]), indicating that women reported this symptom more frequently than men, regardless of diagnostic group.

Two more effects were significant on a trend level: First, there was an interaction effect of group x gender for the item "Unusual difficulties concentrating" ($P = .062$; OR = 0.219 [0.043; 1.069]), which was due to a non-significantly higher frequency of this symptom in male ARMS compared to female ARMS patients ($P = .356$) and a trend-wise significantly higher frequency of this symptom in female FEP compared to male FEP patients ($P = .098$).

Second, there was a trend-wise main effect of gender for the item "Withdrawal, avoiding contacts" ($P = .056$; OR = 2.510 [1.051; 7.373]), indicating that this item tended to be more frequently reported by men than women, regardless of diagnostic group.

3.3 | Most common first self-perceived symptoms: Symptom cluster level

Frequencies of the 14 first self-perceived symptom clusters of the BIP in male and female ARMS and FEP patients are shown in Figure 1.

In the logistic regression models, we found significant main effects of gender in the absence of significant group x gender interactions for the symptom clusters "Worries, agitation, anxiety" ($P = .006$; OR = 0.395 [0.201; 0.769]) and "Hallucinations" ($P = .047$; OR = 0.294 [0.082; 0.974]), indicating that women reported these symptom clusters more frequently than men independent of diagnostic groups. However, as mentioned earlier, the cluster "Hallucinations" includes full-blown as well as sub-threshold symptoms.

Furthermore, there was a significant group × gender interaction for the symptom cluster "Thinking, concentration" ($P = .012$; OR = 0.152 [0.034; 0.652]), which was due to a significantly higher frequency of this symptom cluster in male ARMS compared to female ARMS patients ($P = .014$) and a non-significantly lower frequency in male FEP compared to female FEP patients ($P = .232$).

We also found a significant main effect of diagnostic group for the symptom cluster "Delusions" ($P = .039$; OR = 3.764 [1.190; 18.320]) in the absence of a significant group x gender interaction, indicating that FEP patients reported this symptom cluster more frequently than ARMS patients, independent of gender.

Additionally, there was a trend-wise main effect of diagnostic group for the symptom cluster "Mood, emotions" ($P = .059$; OR = 0.542 [0.281; 1.007]), which was due to a higher frequency of this symptom cluster in ARMS than in FEP patients.

4 | DISCUSSION

In this study, investigating for the first time gender differences in both AMRS and FEP patients in the first self-perceived signs and symptoms at illness onset, only few gender differences were found with women reporting more frequently anxiety and positive psychotic symptoms (single item "Unusual anxiety, fears"; symptom clusters "Worries, agitation, anxiety" and (sub-threshold) "Hallucinations") and men reporting (trend-wise) more frequently negative and cognitive symptoms (single items "Withdrawal, avoiding contacts" and in the ARMS group "Unusual difficulties concentrating"; symptom cluster "Thinking, concentration" only in the ARMS group).

When comparing ARMS and FEP independent of gender, the symptom cluster "Delusions" was more frequently reported by FEP than by ARMS patients while the symptom clusters "Mood, emotion" was more frequently reported by ARMS than FEP patients.

These findings are consistent, at least in part, with the only previous study that has investigated gender differences in first self-

TABLE 2 Most frequently reported first self-perceived signs and symptoms

Rank	Symptom	Frequency	Percentage
ARMS women (*N* = 45)			
1	Depressed, not able to feel joy	13	28.9
2	Unusual anxiety, fears	12	26.7
3	Loss of energy, slow, weak	8	17.8
4	Unusual difficulties concentrating	6	13.3
5	Sleeping problems for more than 1 week	5	11.1
5	Unusually sensitive, thin-skinned	5	11.1
5	Withdrawal, avoiding contacts	5	11.1
ARMS men (*N* = 91)			
1	Depressed, not able to feel joy	23	25.3
2	Unusual difficulties concentrating	18	19.8
3	Withdrawal, avoiding contacts	17	18.7
4	Loss of energy, slow, weak	14	15.4
5	Unusual anxiety, fears	13	14.3
FEP women (*N* = 26)			
1	Unusual difficulties concentrating	6	23.1
2	Depressed, not able to feel joy	5	19.2
2	Unusual anxiety, fears	5	19.2
4	Heard voices when nobody was there	4	15.4
5	More nervous, restlessness	3	11.5
5	More sorrows, not able to stop worrying	3	11.5
5	People tried to harm, poison, chase or kill me	3	11.5
5	Sleeping problems for more than 1 week	3	11.5
5	Unusually frequent headaches, other physical complaints	3	11.5
5	Unusually sensitive, thin-skinned	3	11.5
FEP men (*N* = 63)			
1	Depressed, not able to feel joy	15	23.8
2	Withdrawal, avoiding contacts	14	22.2
3	Irritable, annoyed, unusually quarrelsome	8	12.7
4	Loss of energy, retarded, weak	7	11.1
4	Unusually suspicious	7	11.1

ARMS = at-risk mental state; FEP = first-episode psychosis.

perceived symptoms in FEP patients (Häfner et al., 1995). This study also found higher rates of worrying among the very first self-perceived symptoms in women and found men to report more trouble with thinking and concentration as their first self-perceived symptom, which we could only find in our male ARMS patients.

The above-reported gender differences in first self-perceived symptoms was also reflected in our measures of current symptomatology (i.e., SANS and BPRS), in which men scored higher in negative symptoms and women in (sub-threshold) positive symptoms. Furthermore, these results are in line with some previous studies that have investigated gender differences in current symptomatology separately in ARMS (Barajas et al., 2015; Pruessner et al., 2017; Rietschel et al., 2015; Waford et al., 2015) and FEP patients (Moukas, Gourzis, Beratis, & Beratis, 2010; Thorup et al., 2007). These studies also pointed towards more negative symptoms in men and more (sub-threshold) positive symptoms in women in ARMS and FEP patients. However, as already discussed earlier, other studies could not confirm these findings and did not reveal significant gender differences in the psychopathology of ARMS and FEP patients (e.g., Bertani et al., 2012, Gonzalez-Rodriguez et al., 2014, Kotlicka-Antczak et al., 2016). In an attempt to synthesize the above findings, it might be speculated that small gender differences in symptoms of the emerging disease exist, with more negative and cognitive symptoms in men and more anxiety or affective/ (sub-threshold) positive symptoms in women. However, the size of this effect is probably small, such that differences in the statistical power of the studies led to heterogeneous results. It should be noted that it is possible that more pronounced gender differences might emerge in FEP patients as compared to the ARMS patients due to the more unspecific nature of this latter subsample (Fusar-Poli et al. 2012).

Still, as shown for example by Walder et al. (2013), gender could improve the prediction of psychosis by moderating the influence of other important predictors, such as social functioning and positive psychotic symptoms.

There are also several limitations of our study. First, the BIP items that we used to measure first self-perceived signs and symptoms did not allow differentiating between sub-threshold and full-blown psychotic symptoms. Hence, no final conclusion can be drawn on whether the reported gender difference in the symptom cluster "Hallucinations" was due to sub-threshold or full-blown symptoms. However, given that psychoses usually do not start abruptly (i.e., with full-blown symptoms), it is likely that the hallucinations that were reported as first symptoms were mostly of sub-threshold severity.

Second, despite the attempt to capture first self-perceived symptoms already in the prodromal phase, it needs to be noted that on average there were almost five years between the appearance of first symptoms and the time point of the interview, which may have led to a recall bias. However, as no gender difference was found in our sample regarding DUI, it is not likely that this has influenced the observed gender difference. Last, the smaller number of FEP patients in the present study might have led to a lack of power to detect possible gender differences in this group compared to the larger ARMS sample.

In interpreting these patterns, it should also be kept in mind that awareness of the symptoms and insight into the illness might be impaired in patients suffering from psychosis. According to a recent review by Gerretsen et al. (2014) insight into schizophrenia is especially impaired in first-episode patients, while it is still mostly intact in the premorbid phase. Furthermore, men and women may differ in their symptom awareness, their illness insight and their willingness and ability to report specific symptoms (Berger, Addis, Reilly, Syzdek, & Green, 2012; Riecher-Rössler, 2010). Thus, it is possible that the few observed differences are at least partly due to reporting bias.

In conclusion, this study revealed small gender differences in ARMS and FEP patients, with women reporting trend-wise less frequently negative and cognitive symptoms and significantly more often anxiety and (sub-threshold) positive symptoms than men. In clinical practice, it might be important to also think of an emerging psychotic disorder when women present with anxiety symptoms,

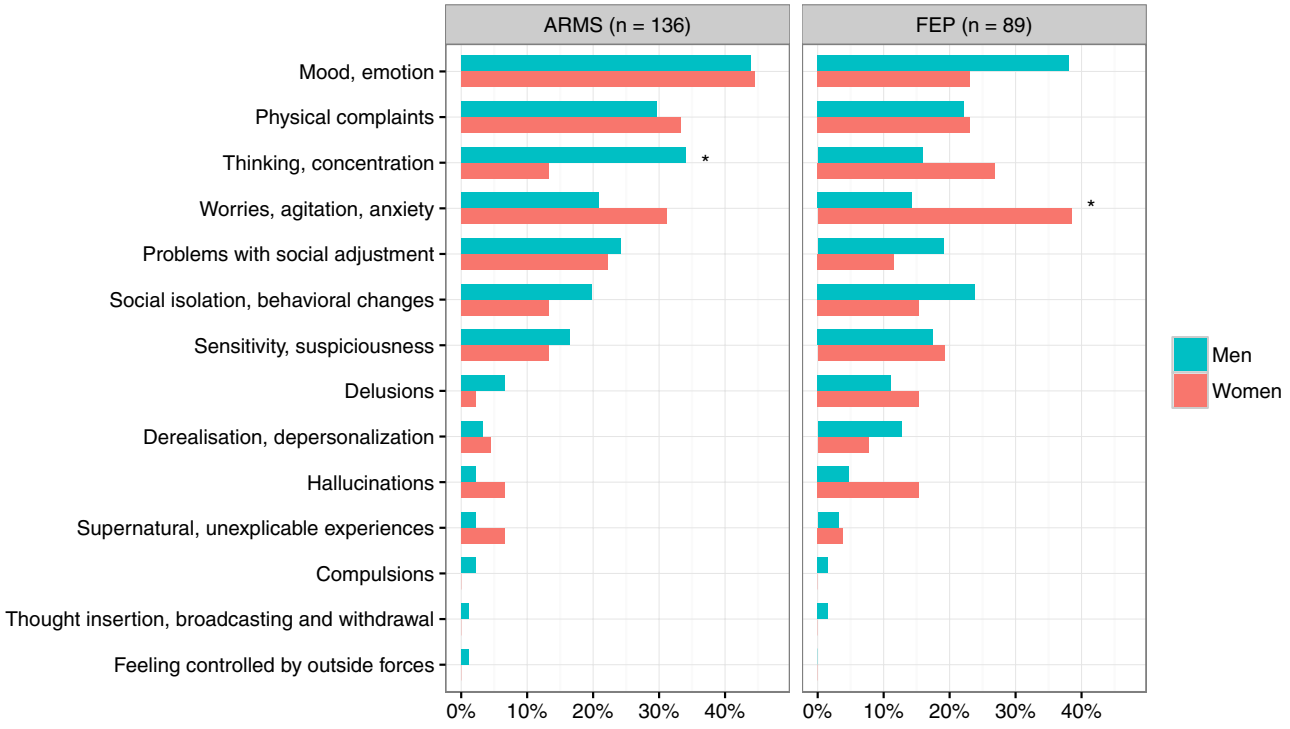

FIGURE 1 Frequencies and gender differences of the 14 first self-perceived symptom clusters of the Basel Interview for Psychosis (BIP) in both diagnostic groups; ARMS = at-risk mental state; FEP = first-episode psychosis; *significant at $P < .05$

because on one hand, these symptoms seem to mark more often the beginning of a psychotic disorder in women than in men, and on the other hand, because they might be more easily misattributed to a depressive disorder in women due to the higher prevalence of depression in women. In men, on the other hand, social withdrawal should be taken more seriously as a potential first sign of emerging psychosis.

ORCID

Anita Riecher-Rössler http://orcid.org/0000-0001-6361-8789

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Discussion

The purpose of the present dissertation was to investigate sex and gender differences with regard to symptomatology, drug use, comorbidity, global functioning, neurocognition and first self-perceived signs and symptoms in patients with emerging psychosis. In the following sections the results of each publication will be discussed.

Gender differences in symptomatology, drug use, comorbidity and functioning

In the first publication, gender differences in symptomatology, drug use, comorbidity (i.e. substance use, affective and anxiety disorders) and global functioning were investigated in a multinational sample of 336 ARMS patients (159 women) presenting for the first time at an early detection service. Regarding psychopathology, our findings are in line with our hypothesis and previous studies among ARMS patients, which have reported no gender differences in psychopathology (Gonzalez-Rodriguez et al., 2014; Willhite et al., 2008). A possible explanation could be that gender differences in the symptoms are so small that they can only be reliably detected in studies with very high statistical power (i.e. in very large datasets or in meta-analyses). Our finding of no gender difference in terms of level of functioning is in line with previous studies (Riecher-Rössler et al., 2018). With regard to drug use and comorbidity, male ARMS patients showed higher rates of current cannabis use and frequency of intake in unadjusted but not in adjusted analyses compared to female ARMS patients. This finding is in accordance with our hypothesis and other studies that report no gender differences regarding substance abuse in the prodromal phase of schizophrenia (Riecher-Rössler et al., 2018; Gonzalez-Rodriguez et al., 2014). Additionally, we found higher rates of comorbid affective and anxiety disorders in female ARMS patients, which is in conflict with a recent study that found no gender differences for affective and anxiety disorders (Rietschel et al., 2015). However, others found greater rates of current depression (Rietdijk et al., 2013; Pruessner et al., 2017) and social anxiety (Rietdijk et al., 2013) in high-risk women, but

the differences reported by Pruessner et al. (2017) did not withstand correction for multiple testing. One possible explanation for the discrepancies in the results could be that the self-report questionnaires used in the study of Rietdijk et al. (2013) have led to an overestimation of the number of patients with an anxiety disorder or depression. Most importantly, our results are in line with those of epidemiological studies on depression and anxiety in the general population (female/male rations of 2:1, respectively) (McLean et al., 2011; Riecher-Rössler et al., 2010b). Hence, it appears that ARMS patients in this respect do not differ from the general population.

Sex differences in cognitive functioning

In the second publication, sex-related neurocognitive performance differences have been investigated in 343 ARMS patients (158 women) and 67 healthy individuals (33 women). All participants completed a comprehensive neurocognitive battery covering the domains of attention/vigilance, reasoning/problem solving, speed of processing, verbal learning and memory, working memory, social cognition and current IQ (for a detailed description, see publication 2). Our finding that women perform better in the domain of verbal learning and memory regardless of whether they were ARMS or HC is in line with our hypothesis and previous research (Riecher-Rössler et al., 2018; Fusar-Poli et al., 2012c). The results corroborate the findings of an earlier study of our own group that reported no interaction effect between diagnostic group (i.e. ARMS, FEP, HC) and verbal learning and memory (Ittig et al., 2015). Additionally, we found that women perform better than men in tasks measuring processing speed (i.e. Trail Making Test, WAIS-III Digit Symbol subtest) independent of group. This finding is consistent with earlier findings from the general population (e.g. Burns et al., 2005; Jorm et al., 2004) and schizophrenia patients (Vaskinn et al., 2011; Torniainen et al., 2011) but in conflict with a previous study that reported a shorter reaction time for men in the working memory task independent of diagnostic group (i.e. ARMS, FEP, HC) (Ittig et al., 2015). A

possible explanation for these inconsistent results could be that the latter did not include tests specifically measuring processing speed.

Gender differences in first self-perceived signs and symptoms

The third publication 'Gender differences in first self-perceived signs and symptoms in patients with an at-risk mental state and first-episode psychosis' is the first study investigating gender differences in both ARMS and FEP patients in the first self-perceived signs and symptoms at illness onset. In total, 136 ARMS (45 women) and 89 FEP patients (26 women) completed the BIP items regarding first self-perceived signs and symptoms and thus were included into the study. In line with our hypothesis, we found only few and relatively small gender differences in the first self-perceived signs and symptoms. Initially, men mainly noticed negative and cognitive symptoms, while women first noticed (sub-threshold) positive and affective symptoms. These findings are partly in line with the only previous study investigating first self-perceived symptoms in FEP patients (Häfner et al., 1995b). The authors reported more worrying in women and more trouble with thinking and concentration in men. Furthermore, our results are in line with more recent studies investigating gender differences in the current symptomatology in ARMS (Barajas et al., 2015; Pruessner et al., 2017; Rietschel et al., 2015; Waford et al., 2015) and FEP patients (Moukas et al., 2010; Thorup et al., 2007). These studies also pointed towards more negative symptoms in men and more (sub-threshold) positive symptoms in women in ARMS and FEP patients. However, as already mentioned above, other studies did not find any significant gender differences in the psychopathology of ARMS and FEP patients (e.g. Bertani et al., 2012; Gonzalez-Rodriguez et al., 2014; Kotlicka-Antczak et al., 2016). According to previous research and our own findings (see publication 1), it might be speculated that small gender differences exist regarding symptomatology, with more negative and cognitive symptoms in men and more anxiety or affective/(sub-threshold) positive symptoms in women. However, the size of this effect is probably small, such that

heterogeneous results might be explained by differences in the statistical power of the studies. It should also be noted that gender differences might be more pronounced in FEP patients compared to ARMS patients due to the larger diagnostic heterogeneity of the latter group (Fusar-Poli et al., 2012b).

Conclusion and Perspectives

In conclusion, the results of the first study indicate that gender differences in symptomatology and comorbidity in ARMS are similar to those seen in frank psychosis and in healthy controls. However, these differences seem to be so small that they would only be reliably detected in studies with very high statistical power (i.e. in very large datasets or in meta-analyses). Such small effects would likely not be clinically meaningful. Future studies should investigate gender differences in symptomatology in studies with very high statistical power.

The results of the second study suggest that sex differences in cognitive functioning in ARMS patients are similar to those seen in the general population and in schizophrenia patients. However, the effects were small which could also be explained by the fact that our neuropsychological test battery was originally selected to identify gene-environment interactions in psychosis rather than detecting sex differences. Accordingly, our test battery did not include one of the most sensitive tasks to detect sex differences such as visuo-spatial tasks. Furthermore, future studies should also take the menstrual status into account since neuropsychological performance has been shown to fluctuate with the monthly cycle (Riecher-Rössler et al., 2018; Hampson, 1990).

The third study revealed small gender differences in the very first self-perceived signs and symptoms of ARMS and FEP patients, with women reporting significantly more often anxiety and (sub-threshold) positive symptoms and men reporting trend-wise more often negative and cognitive symptoms. Clinically, it might be important to think of an emerging psychotic disorder when women present with anxiety symptoms. On one hand, these symptoms seem to

mark more often the beginning of a psychotic disorder in women compared to men and on the other hand, they might be misattributed to a depressive disorder in women because of the higher prevalence of depression in women. In men, however, social withdrawal might be a first sign of emerging psychosis and should be taken more seriously by clinicians.

Altogether, the current dissertation reveals few sex and gender differences in all three publications. Gender differences regarding symptomatology in ARMS – if present at all – are small and similar to those found in frank psychosis and healthy controls. Similar sex differences regarding cognitive functioning can be found in the prodromal phase of psychosis, which also at least partly resembling those of the general population. Furthermore, the results from publication three again suggest that only few and relatively small gender differences exist in the first self-perceived signs and symptoms of the disease. More methodologically sound research should be done, investigating both sex (biological) and gender (psychosocial) to identify potential differences in psychopathology and neurocognition in emerging psychoses.

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Curriculum Vitae

Last name	Menghini-Müller
First name	Stephanie Pascale
Date of birth	12th June 1989
Home town	Lenzburg AG

EDUCATION

Since 02.2015	**PhD Candidate** Department of Psychology, Division of Clinical Psychology and Epidemiology, University of Basel, Switzerland
02.2015 – 03.2019	**Postgraduate degree in Psychotherapy** Academy of Behavioral Therapy and Methods Integration (AIM), Zurich, Switzerland
09.2012 – 06.2014	**Master of Science in Psychology** **Majoring in Clinical Psychology and Neuroscience** Department of Psychology, Division of Clinical Psychology and Psychotherapy, University of Basel, Switzerland
09.2008 – 12.2011	**Bachelor of Science in Psychology** Department of Psychology, University of Basel, Switzerland
08.2002 – 06.2007	**General Qualification for University Entrance** Wirtschaftsgymnasium, Basel, Switzerland

WORK EXPERIENCE

Since 10.2019	**Clinical Psychologist and Psychotherapist** Center for Anxiety and Depression Zurich (ZADZ), Switzerland
03.2017 – 06.2018	**Clinical Psychologist and Psychotherapist** Outpatient Clinic A and B, Luzerner Psychiatrie, Switzerland
07.2016 – 02.2017	**Stay abroad**, Perth, Australia
02.2015 – 07.2016	**Assistant Psychologist and PhD Candidate** Center for Gender Research and Early Detection**,** University of Basel Psychiatric Hospital (UPK), Switzerland
03.2014 – 06.2014	**Internship** Department of Psychiatry, Hospital Affoltern a.A., Switzerland

03.2014 – 12.2014	**Master Project in Psychooncology** Department of Gynaecology and Obstetrics, University Hospital Basel, Switzerland
06.2012 – 08.2012	**Internship in Social Medicine and Psychosomatics** Department of Gynaecology and Obstetrics, University Hospital Basel, Switzerland

PERSONAL SKILLS

Languages	German	Mother tongue
	English	Excellent knowledge
	French	Good knowledge
Software	Microsoft Office; Open Office R; IBM SPSS Software EndNote	

RESEARCH OUTPUT LIST

Publications in peer-reviewed scientific journals

Menghini-Müller S, Studerus E, Ittig S, Valmaggia LR, Kempton MJ, van der Gaag M, de Haan L, Nelson B, Bressan RA, Barrantes-Vidal N, Jantac C, Nordentoft M, Ruhrmann S, Sachs G, Rutten BP, van Os J, Riecher-Rössler A, EU-GEI High Risk Study Group. Sex differences in cognitive functioning of patients at-risk for psychosis and healthy controls - Results from the EU-GEI study. European Psychiatry, **2020**; 63(1); e25: 1-9. http://dx.doi.org/10.1192/j.eurpsy.2019.10

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