Depression and social anxiety in help-seeking patients with an ultra-high risk for developing psychosis

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Abstract

Background
Knowledge on associations between ultra-high risk (UHR) for developing psychosis and on non-psychotic psychopathology in help-seeking populations is limited with respect to differences between male and female patients. The present study tests the hypothesis that both social anxiety and depression are highly prevalent in an UHR population, particularly among women.

Method
From February 2008 to February 2010 baseline data were collected from help-seeking subjects (14–35 years) who were included in the Dutch Early Detection and Intervention Evaluation (EDIE-NL) trial. Two recruiting strategies were used: a two-stage screening strategy in a population of consecutive help-seeking and distressed subjects of secondary mental health services, and a referral strategy.

Results
This study included 201 patients with a mean age of 22.7 years. Of these, 102 (51%) were female. 58% of the patients met the criteria for clinical depression on the Beck Depression Inventory and 42% met the criteria for clinical social phobia on the Social Interaction Anxiety Scale.

Discussion
Women showed more depression and social anxiety than men. The results support the hypothesis that UHR is associated with depression and social anxiety, particularly in women. Screening a help-seeking population with depression and anxiety may be effective in detecting patients at UHR for developing psychosis.
Introduction

The first psychotic episode is, in retrospect, generally preceded by a prodromal phase. In prospective studies this phase has been termed the At-Risk Mental State (ARMS) stage. This group of patients is at ultra-high risk (UHR) for developing a psychotic episode. ARMS is associated with the presence of both lifetime and current comorbid disorders (1). The development of affective psychopathology, particularly mood and anxiety disorders, is considered to be a prodromal sign for the development of psychotic disorders (2–7). Häfner et al. (8,9) found that the prodromal stage of both schizophrenia and unipolar depression is marked by the development of symptoms and signs of depression, followed by the onset of negative symptoms and finally the development of psychotic symptoms. Functional and social impairment may also develop alongside these symptoms. Birchwood et al. (10) found anxiety to be a prodromal sign in a retrospective study with first episode psychosis patients. Additionally, paranoid ideation and social anxiety were found to be overlapping syndromes in a heterogeneous non-psychotic clinical sample (11).

Reviews have shown that the pathways to psychosis in first-episode schizophrenia patients are gender specific. Negative symptoms and cognitive impairments are more often associated with the onset of psychotic disorders in males, while affective symptoms and help-seeking characterize the development of psychosis in females (12,13). However, in a retrospective study on first episodes psychosis patients Häfner et al. (14) found no differences for gender in the earliest prodromal signs. In a prospective study, there were no significant gender differences in demographic variables, symptoms or functioning at baseline. Males were found to have significantly higher levels of negative symptoms and marginally lower levels of functioning when baseline and follow-up time points were considered together. Females reported higher levels of social support at baseline (15).

The present study explores the presence of depressive and social anxiety symptoms in a large UHR sample, using the baseline characteristics of help-seeking patients included in the Dutch Early Detection and Intervention Evaluation (EDIE-NL) psychosis prevention study (16). The study used a two-stage screening strategy in a general help-seeking population entering secondary mental healthcare services, and a referral strategy to a specialized academic center offering tertiary care. The screening strategy detected relatively more women with ARMS (17). As a result, the sex distribution in the EDIE-NL cohort is about equal and makes it more easy to compare female and male patients on the presence of depressive and social anxiety symptoms.

For the present study two hypotheses are tested: (1) that the severity of subclinical psychotic symptoms is associated with the intensity of depressive and social anxiety symptoms, and (2) that female patients have more severe depressive and social anxiety symptoms than male patients.
Method

Study design
EDIE-NL is a longitudinal randomized controlled trial that compared Treatment As Usual (TAU) to an add-on cognitive behavioral therapy targeting psychosis-risk symptoms (CBT+TAU). A comprehensive description of the study, its aims and protocol have been described elsewhere (16).

The design of this study was approved by the Dutch Association of Medical Research Ethics Committees (NVMETC) for mental health organizations. The trial was conducted in compliance with the World Medical Association Declaration of Helsinki (Edinburgh amendment, 2000) (18). The trial is registered at Current Controlled trials as trial number ISRCTN21353122. Informed consent was obtained in writing from all participants. In addition, the parents gave written informed consent for subjects aged ≤ 18 years.

Instruments

The Prodromal Questionnaire (PQ)
Prodromal symptoms were screened and assessed with the PQ (19); authorized Dutch translation by van der Gaag, Klaassen and Wunderink). The PQ is a 92-item self-report questionnaire that assesses the presence of lifetime prodromal symptoms on a two-point scale (true/false). Based on the results of a pilot study, we set the cut-off using a ROC curve for inclusion and subsequent CAARMS interview at a score of 18 on the 45 positive symptom items of the PQ.

The Comprehensive Assessment of At Risk Mental State (CAARMS)
At-risk mental state was assessed with the CAARMS (20), including the Social and Occupational Functioning Assessment Scale (SOFAS) (21). The CAARMS is a semi-structured interview conducted to determine the presence, severity (0–6), frequency (0–6), distress (0–100) and type of ARMS symptoms (i.e. unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganized speech). This instrument uses the severity and frequency of ARMS symptoms to discriminate between ARMS, psychosis, or neither of both, with high reliability and validity (86% sensitivity, 91% specificity). Prof. A. R. Yung (who developed the CAARMS interview) gave the researchers extensive training in the use of this instrument. Reliability checks of the Dutch version of the CAARMS were performed about every 3 months during the study. The pair-wise inter-rater concordance of the CAARMS was 0.81.

The Beck Depression Inventory-II (BDI-II) and Calgary Depression Scale (CDS)
Depression was assessed with both the Dutch translation of the BDI-II (22,23) and the CDS (24,25). Scores on the BDI range from 0 to 63 (0–13 = minimal depression; 14–19 = mild
depression; 20–28 = moderate depression; 29–63 = severe depression). Clinical depression is defined as BDI score >19. The CDS is a 9-item interview that assesses depressive symptoms separately from the negative symptoms of schizophrenia.

The Social Interaction Anxiety Scale (SIAS)
Social anxiety was measured with the SIAS (26). This is a 20-item self-report questionnaire measuring social phobia and social anxiety disorder. Experiences in social situations are rated on a 5-point scale ranging from 0 (not at all characteristic of me) to 4 (extremely characteristic of me). A score of 36 or more represents social phobia.

Demographic characteristics
Social demographic characteristics were assessed with a demographic questionnaire, designed by the researchers. Variables were chosen on the basis of previous research and known risk factors for psychotic disorders.

Subjects and procedure
Baseline data were collected from help-seeking patients who entered secondary and tertiary mental healthcare between February 2008 and February 2010 and were included in the EDIE-NL trial (16). The consecutive help-seeking populations entering secondary mental healthcare services were pre-screened with the PQ (19). Subjects who scored above the cut-off score of 18 on the relevant items of the PQ and below 65 on the Global Assessment of Functioning (GAF) (27) were assessed with the CAARMS interview (20). In addition, all patients referred to tertiary mental healthcare, who were suspected of development towards florid psychosis or a first psychotic episode of schizophrenia spectrum disorders, were assessed with both the PQ and the CAARMS.

The UHR population consists of three groups as defined by the PACE criteria (6):
patients with a schizotypal personality disorder or a first-degree relative with psychosis (genetic risk group);
patients experiencing attenuated positive symptoms, such as ideas of reference, odd beliefs, magical thinking, or unusual perceptual experiences; and
patients experiencing a brief psychotic episode of ≤1 week in duration that resolves without antipsychotic medication (Brief Limited Intermittent Psychotic Symptoms: BLIPS).

In addition, in all groups social functioning as assessed with the SOFAS (21) had to be impaired, defined as a SOFAS score of ≤50 over the last year and/or a drop in the SOFAS score of 30% during at least 1 month in the past year.

Exclusion criteria were: (a) current or previous usage of a cumulative dose of antipsychotic medication of in total ≥15 mg haloperidol equivalent (e.g. maximum of 5 days of 3 mg); (b) severe learning impairment; (c) psychiatric symptoms due to a somatic condition; (d)
insufficient competence in the Dutch language; (e) a history of psychosis. A total of 864 patients with a score ≥18 on the PQ (subclinical) positive symptoms were interviewed with the CAARMS. Of these, 104 patients reported symptoms above the psychosis threshold; 302 patients fulfilled the ARMS criteria. Of these 302 patients, 201 signed informed consent and were included in the present study.

**Statistical analysis**

Baseline characteristics were explored using the SPSS version 18.0 (Statistics UK). Chi-square statistics were used to investigate gender differences with respect to fulfilling the criteria of a clinical depression or anxiety disorder. MANCOVA was conducted to explore differences between both the sexes on depressive symptom scores and social anxiety scores. The analysis was corrected for ethnicity and age, as these characteristics were associated with affective disorders in this sample (17,28). MANCOVA corrects for error type I and II, that are associated with multivariate testing. Pearson’s correlation and linear regression analyses were conducted to investigate associations between the CAARMS positive items total score and the BDI and SIAS scores respectively.

**Results**

The study sample included 201 UHR patients; their mean age was 22.7 (S.D. 5.52) years, 51% was female and almost 40% belonged to an ethnic minority (Table 1). Over 80% of the patients were included due to attenuated symptoms, and 14% met the criteria for two inclusion groups.

**ARMS symptoms and psychopathology**

Of the UHR patients, 58% met the criteria for clinical depression on the BDI and 42% met the criteria for social phobia as assessed with the SIAS. Additionally, we analyzed gender separately and found 45.5% of the men met clinical depression versus 70.6% of the women ($\chi^2$ (d.f.=1) =13.05, $p <0.001$). A total of 35.4% of the men and 49.0% of the women met the criteria for social anxiety ($\chi^2$ (d.f.=1) =3.85, $p=0.05$) (See Table 1).

**Hypothesis 1** stated that subclinical positive symptoms and symptoms of anxiety and depression are associated. This was tested with regression analyses. Age, gender and ethnicity are added as these are confounding variables. Step-wise regression analyses with positive symptoms as dependent variable and BDI, SIAS, age, gender and ethnicity as predictor variables showed that a higher total score on positive CAARMS symptoms was associated with a higher score on the SIAS ($t=2.927$, $p=0.004$).
Additional regression analyses were conducted with depression and anxiety as dependent variables. Step-wise regression analyses with BDI scores as dependent variable and positive symptoms, SIAS, age, gender and ethnicity as predictor variables showed that a higher total score on depression symptoms was associated with a higher score on the SIAS ($t=10.30$, $p=0.000$), higher age ($t=3.65$, $p=0.000$), and female sex ($t=2.26$, $p=0.025$).

Table 1. Socio-demographic characteristics of the EDIE.NL sample

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, SD (range)</td>
<td>22.7, SD = 5.52 (14-35)</td>
</tr>
<tr>
<td>Female</td>
<td>102 (50.7%)</td>
</tr>
<tr>
<td>Single</td>
<td>149 (74.1%)</td>
</tr>
<tr>
<td>Payed job</td>
<td>82 (40.8%)</td>
</tr>
<tr>
<td>Unpaid job</td>
<td>14 (7.0%)</td>
</tr>
<tr>
<td>Attending school</td>
<td>57 (28.4%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>N (%)</td>
</tr>
<tr>
<td>Dutch</td>
<td>114 (56.7%)</td>
</tr>
<tr>
<td>Moroccan</td>
<td>22 (10.9%)</td>
</tr>
<tr>
<td>Turkish</td>
<td>13 (6.5%)</td>
</tr>
<tr>
<td>Surinamese</td>
<td>16 (8.0%)</td>
</tr>
<tr>
<td>Other western</td>
<td>14 (6.9%)</td>
</tr>
<tr>
<td>Other non-western</td>
<td>22 (10.9%)</td>
</tr>
<tr>
<td>CAARMS inclusion</td>
<td>N (%)</td>
</tr>
<tr>
<td>Genetic risk only</td>
<td>7 (3.5%)</td>
</tr>
<tr>
<td>APS only</td>
<td>163 (81.1%)</td>
</tr>
<tr>
<td>BLIPS only</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Genetic risk + APS</td>
<td>27 (13.4%)</td>
</tr>
<tr>
<td>APS + BLIPS</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Clinical Depression (BDI &gt;19)</td>
<td>117 (58.2%)</td>
</tr>
<tr>
<td></td>
<td>45 male/72 female</td>
</tr>
<tr>
<td>Social anxiety (SIAS &gt; 36)</td>
<td>85 (42.3%)</td>
</tr>
<tr>
<td></td>
<td>35 male/50 female</td>
</tr>
</tbody>
</table>

*Note: APS, attenuated psychotic symptoms; BLIPS, brief limited and intermittent psychotic symptoms BDI, Beck depression inventory; SIAS, Social Interaction Anxiety Scale.*
Step-wise regression analyses with SIAS scores as dependent variable and positive symptoms, BDI, age, gender and ethnicity as predictor variables showed that a higher total score on anxiety symptoms was associated with a higher score on the BDI ($t=11.97, p=0.000$), and a higher score on positive symptoms ($t=1.99, p=0.048$).

Furthermore, within gender regression analyses were conducted. Regression analysis with male patients showed that age predicted positive symptom score ($t=2.630, p=0.010$). Regression analysis with female patients showed that anxiety predicted positive symptom score ($t=2.104, p=0.038$).

### Gender and psychopathology

Table 2 shows the age, positive symptoms, anxiety and depression scores for male and female patients and for those subjects who fulfilled the criteria for an anxiety disorder or a clinical depression. Anxiety and depression are associated with older age. Females have significantly higher anxiety and depression scores than males.

Age and being a member of a minority group are associated with psychopathology in this sample (28). Table 3 shows the Pearson correlations between psychopathology, age, gender and ethnicity. A MANCOVA was conducted with gender as the fixed variable and SIAS and BDI as dependent variables with age and ethnicity as covariates. There were gender differences on anxiety and depression scores, with the female patients demonstrating the highest symptom scores (See Table 4).

### Table 2: The difference between male and female patients and between those who fulfill criteria for clinical anxiety disorder or depression

<table>
<thead>
<tr>
<th></th>
<th>Male mean (SD)</th>
<th>Female mean (SD)</th>
<th>SIAS&gt;36 mean (SD)</th>
<th>BDI&gt;19 mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21.34 (5.47)</td>
<td>22.02 (5.62)</td>
<td>23.32 (5.44)</td>
<td>24.58 (5.49)</td>
</tr>
<tr>
<td>PS score</td>
<td>10.15 (8.79)</td>
<td>10.44 (6.73)</td>
<td>10.76 (7.04)</td>
<td>10.64 (7.46)</td>
</tr>
<tr>
<td>SIAS score</td>
<td>28.93 (16.50)</td>
<td>34.49 (16.99)</td>
<td>48.69 (8.22)</td>
<td>39.88 (14.45)</td>
</tr>
<tr>
<td>BDI score</td>
<td>19.87 (12.13)</td>
<td>23.07 (11.95)</td>
<td>30.11 (10.25)</td>
<td>31.31 (7.93)</td>
</tr>
<tr>
<td>Dutch</td>
<td>52.9%</td>
<td>47.1%</td>
<td>35.3%</td>
<td>49.6%</td>
</tr>
<tr>
<td>Non-Dutch</td>
<td>43.9%</td>
<td>56.1%</td>
<td>51.3%</td>
<td>70.0%</td>
</tr>
</tbody>
</table>

Note: PS-score, CAARMS subclinical positive symptoms score; BDI score, Beck Depression Inventory score; SIAS score, Social Interaction Anxiety Scale score.
Table 3. The association of psychopathology with gender, age and ethnicity

<table>
<thead>
<tr>
<th></th>
<th>BDI r (p-value)</th>
<th>SIAS r (p-value)</th>
<th>Positive symptoms r (p-value)</th>
<th>Age r (p-value)</th>
<th>Dutch Non-Dutch r (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>.226 (.001)</td>
<td>.164 (.020)</td>
<td>.051 (.475)</td>
<td>.075 (.291)</td>
<td>.089 (.210)</td>
</tr>
<tr>
<td>BDI</td>
<td>1</td>
<td>.660 (.000)</td>
<td>151 (.034)</td>
<td>.406 (.000)</td>
<td>.233 (.001)</td>
</tr>
<tr>
<td>SIAS</td>
<td>1</td>
<td>204 (004)</td>
<td>.346 (.000)</td>
<td>.217 (002)</td>
<td>1</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>1</td>
<td>.147 (.037)</td>
<td>-.049 (493)</td>
<td>1</td>
<td>.311 (.000)</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: BDI, Beck Depression Inventory; r, Pearson correlation; SIAS, Social Interaction Anxiety Scale

Table 4. MANCOVA results of depression and anxiety symptom scores across both sexes with age and ethnicity as covariates

<table>
<thead>
<tr>
<th></th>
<th>Total N=201 Est. Mean (st. error)</th>
<th>Male, N=99 Est. Mean (st. error)</th>
<th>Female, N=102 Est Mean (st. error)</th>
<th>F-value</th>
<th>d.f.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>216 (.85)</td>
<td>189 (.121)</td>
<td>244 (.120)</td>
<td>774</td>
<td>1, 184</td>
<td>.010</td>
</tr>
<tr>
<td>SIAS</td>
<td>31.7 (118)</td>
<td>28.9 (169)</td>
<td>33.5 (167)</td>
<td>440</td>
<td>1, 184</td>
<td>.040</td>
</tr>
<tr>
<td>CDS</td>
<td>6.2 (.35)</td>
<td>4.97 (.49)</td>
<td>7.49 (.48)</td>
<td>13.63</td>
<td>1, 184</td>
<td>.000</td>
</tr>
</tbody>
</table>

Note: BDI, Beck Depression Inventory; SIAS, Social Interaction Anxiety Scale; CDS, Calgary Depression Scale.

Discussion

The present study explored the association between At Risk Mental States (ARMS) and symptoms of depression and social anxiety. The studied sample was help-seeking for several axis 1 and/or axis 2 disorders, with mood disorders and anxiety disorders as the most prevalent diagnoses. Overall, 58% of the patients had a clinical depression measured by the Beck Depression Inventory (BDI) and 42% of the patients showed clinical social phobia on the Social Interaction Anxiety Scale (SIAS). Both sexes showed similar scores for intensity and frequency of the positive symptoms measured by the Comprehensive Assessment of At Risk Mental States (CAARMS). The present study shows that the subclinical psychotic symptoms are associated with anxiety and not with depression. This is specifically so in female patients.
Thus, the first hypothesis is partially supported. Female patients showed higher anxiety and depression scores and therefore, the second hypothesis was supported.

The predominance of women in the clinical depression and anxiety disorder groups was expected as reviews have shown that affective symptoms and help-seeking is associated with psychosis in women (12,13). In addition, it is suggested that the symptom differences between the sexes are the result of an exaggeration of the regular gender differences in the general population. Women are more often help-seeking than men and women experience more often anxiety and mood disorders whereas men more often report addiction. Our results are in line with previous studies reporting that depression is associated with psychosis (2,8,9). A recent meta-analysis found that 41% of the UHR subjects had a depression (range 16–64%) and that 15% showed an anxiety disorder (range 8–39%) according to the DSM/SCID criteria (29). These percentages are lower than in the current study although the percentage is still within the range. An explanation could be that we used self-report questionnaire scores that probably overestimate the number of subjects with a disorder. Morrison et al. (30) reported higher SIAS scores in an UHR cohort than in this study (mean SIAS about 42) and reported that 58% of the UHR subjects scored above the threshold of an anxiety disorder.

Although the current study shows that depression and anxiety disorders are prevalent disorders, it also shows that ARMS- patients were referred to several care programs treating a variety of axis 1 and axis 2 disorders. These results are in accordance with other studies reporting that the ARMS stage is also marked by the presence of both lifetime and current comorbid disorders (1,31). However, the latter study suggested that the nature of comorbidity did not differ from the presence of comorbidity in patients suffering mental health problems without prodromal signs for schizophrenia. Furthermore, anxious and depressed patients have a higher prevalence of subclinical psychotic symptoms (32).

**Population characteristics**

In the present study, the total score on positive CAARMS symptoms was similar in men and women. This is probably a result of the inclusion criteria. This study included patients within a small range of severity on subclinical CAARMS symptoms. Moreover, the positive symptoms in both sexes were similar to symptoms in other ARMS-cohorts, which included a higher percentage of men than women (33). The present results are supported by epidemiological studies reporting that the core symptoms of schizophrenia are similar for both sexes, although the mean age at onset of psychosis was 3–4 years later in females (34). This might explain the differences in clinical presentation once psychosis is present: typical schizophrenia has an early onset in a majority of male patients, while atypical schizophrenia with more mood symptoms and better prognosis is late onset with a majority of female patients (35).
Strengths and limitations

The results of the present study need to be interpreted in the light of some limitations. The first concerns the study cohort. All included patients were participants in the EDIE-NL trial and these participants are a selection of the ARMS-patients, because some patients refused to participate. Therefore, this selection may not be representative for all ARMS-patients. Secondly, because self-report questionnaires were used to assess depression and social anxiety this could result in over-reporting of symptoms. However, self-report is considered to be reliable in help-seeking and general populations (36,37), and the reliability and validity of the questionnaires used are good. The strong internal/external validity of the detection strategies is a strength of this study. The screening recruitment strategy combined with referral resulted in equal proportions of male and female patients. As our study included a large number of ARMS-patients, the statistical power to explore gender differences in depressive and social anxiety symptoms was high.

Conclusions and clinical implications

In the present study we found that 58% and 42% of the ARMS patients met criteria of clinical depression and social phobia. This implies that having an at-risk mental state is often accompanied by depression and social anxiety. Anxiety and not depression is associated with the level of subclinical psychotic symptoms, particularly in female patients. Overall, female patients showed higher levels of anxiety and depression than male patients.

Acknowledgments

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References


