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A comparison of depressive symptom profiles between current major depressive disorder and schizophrenia spectrum disorder

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ABSTRACT

Introduction: Depressive symptoms are highly prevalent and clinically relevant in schizophrenia spectrum disorder (SSD) patients. So far, little is known about to what extent the depressive symptom profile in SSD is comparable to that seen in major depressive disorder (MDD).

Methods: Data were derived from the Genetic Risk and Outcome of Psychosis study (GROUP) and the Netherlands Study of Depression and Anxiety (NESDA). We examined differences in severity of depressive symptom profiles and distribution of mood/cognition and somatic/vegetative depressive symptoms using the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR) within SSD patients (n = 449), MDD patients (n = 816) and healthy controls (n = 417), aged 18 to 50. Within SSD, associations between depression severity and clinical and demographic data were examined.

Results: 60.4% of SSD patients showed substantial depressive symptomatology (QIDS-SR≥6). The difference in mood/cognition symptoms between SSD and MDD was larger (higher symptoms in MDD, effect size = 1.13), than the differences in somatic/vegetative symptoms (effect size 0.74). In patients with SSD, multivariable regression analyses showed that lower social functioning, male gender, use of benzodiazepine and more severe positive symptoms were associated with higher overall depressive symptomatology. The use of antipsychotics or antidepressants was associated with more somatic/vegetative symptoms.

Conclusion: More than half of SSD patients have considerable depressive symptomatology, with a relative preponderance of somatic/vegetative symptoms compared to the profile seen in MDD. Future research could explore whether depressive symptom profile in SSD may also be associated with biological dysregulations like in MDD.

1. Introduction

Depressive symptoms have shown substantial impact on prognosis and wellbeing of persons with schizophrenia spectrum disorders (SSD) (Upthegrove et al., 2017), with a recent systematic review and meta-analysis reporting a prevalence rate of 43.9% (Herniman et al., 2019). The diagnoses of 'schizoaffective disorder' and 'mood disorder with psychotic features', and shared risk factors (Häfner et al., 2005b), suggest shared aetiology (Emsley et al., 1999; Häfner et al., 2005b; Hoffmann et al., 2017; Rabany et al., 2011). Furthermore, SSD and Major Depressive Disorder (MDD) show similarities in symptoms presented during prodromal stages (Häfner et al., 2005b), suggesting depressive symptomatology to be part of the core psychopathology of early SSD (Häfner et al, 2005a, 2005b; Schennach et al., 2015).

Next, depressive symptoms have been found to be a marker of poor course trajectories in SSD (Maurer et al., 2006). Häfner et al. (2005a) found that patients suffering from more depressive symptoms in prodromal stages of illness had higher SSD symptom severity at the onset of first psychosis. Likewise, SSD patients with higher severity of co-occurring depressive symptoms tend to have a poorer clinical and social outcome (Dollfus et al., 2000), lower quality of life (Sönmez et al., 2016), less favourable personal recovery (Van Eck et al., 2018), lower levels of medication adherence (Conley et al., 2007; Hawton et al., 2005; Hou et al., 2016), poorer physical health status (Conley et al., 2007) and

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an increased risk for suicide (Cavelti et al., 2012).

In studies on MDD, it was demonstrated that mood/cognition and somatic/vegetative domains could be distinguished (Schaakxs et al., 2017; Wardenaar et al., 2010). These domains may be associated with different underlying pathophysiological pathways, and increasing evidence suggests that these domains could partly explain heterogeneity in biological dysregulation among MDD patients (Penninx, 2017; Penninx et al., 2013). To date, only three studies compared depressive symptoms between SSD and MDD patients. Häfner and colleagues (2005b, 2005a) and Rahim and Rashid (2017) showed that the symptom 'depressed mood' was more pronounced in depressive disorder, whereas Rahim and Rashid (2017) also showed that symptoms of sleep and appetite disturbances were more pronounced in schizophrenia. These findings were limited by different screening tools used between groups and relatively small sample sizes (up to 130 patients), warranting replication in larger cohorts, using a single instrument to assess severity of depressive symptoms across diagnostic categories.

In recent years, several studies have evaluated associations between depressive symptoms and other clinical and demographic characteristics in SSD. Greater severity of depressive symptoms was found to be associated with both higher severity of positive as well as negative symptoms (Herniman et al., 2019), with most robust associations found for positive symptoms and contradicting findings for negative symptoms (Krynicki et al., 2018). Moreover, associations between all three subdomains appear to be depending on associations between individual symptoms (van Rooijen et al., 2018). Next, a range of risk factors was identified such as family history of mood disorders, peri- and postnatal complications in brain development, and neuroticism (Hou et al., 2016) and with other clinical characteristics such as alcohol abuse (Cotton et al., 2012; Fond et al., 2018), anxiety (Hou et al., 2016; Huppert et al., 2001), and lack of social support (Baynes et al., 2000). Antipsychotic medications have been reported to cause depression like symptoms such as subjective unwellbeing (De Haan et al., 2003; 2000), sleep alterations (Chan et al., 2017), weight gain (Huhn et al., 2019) and increase of appetite (Henderson et al., 2015). However, recent research has also found antipsychotic medication to be useful in the treatment of depressive symptoms in SSD (Gregory et al., 2017; Huhn et al., 2019). Also, associations have been found between benzodiazepine use and depressive symptoms in SSD (Fond et al., 2018; Hoertel et al., 2019). To date, some of these findings of associated variables are inconsistent, and comparison of studies is hampered by different designs and methods, warranting further investigation into a comprehensive set of factors associated with depressive symptoms in SSD.

To summarize, depressive symptoms are highly prevalent and greatly impact on illness course and quality of life of persons with SSD. From extensive research in MDD patients, we know that two types of depressive symptom domains that are probably associated with biological dysregulation can be distinguished: mood/cognition and somatic/vegetative domains.

To the best of our knowledge, this is the first, large cohort study in which persons with SSD and MDD and healthy controls are compared on depressive symptom profiles using the same assessment instrument.

The first aim of this study is to compare overall depression severity and severity of the two symptom domains between healthy controls, SSD and MDD. In addition, the distribution of these domains on the item level was further explored by comparing the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) (Rush et al., 2003) items between SSD and MDD. Finally, we investigated associations between different depressive symptom profiles in persons with SSD and clinical and social characteristics.

2. Methods

2.1. Participants

Data were derived from the Dutch multicentre 'Genetic Risk and Outcome of Psychosis' (GROUP) study (Korver et al., 2012) and from the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008). Details of both studies were described earlier (see Korver et al., 2012; Penninx et al., 2008). The GROUP study was approved by the Medical Ethics Committee of the University of Utrecht and subsequently by local review boards of each participating medical center, and NESDA was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam. All respondents provided written informed consent.

In short, GROUP is a longitudinal and observational study which consists of 1129 patients with SSD, 1057 siblings, 919 parents and 590 healthy controls, aged between 16 and 50 years, and was designed to examine the genetic and environmental factors contributing to the development of a psychotic disorder. Potentially eligible persons, presenting themselves consecutively at regional psychosis departments or academic centers as either outpatients or inpatients, were identified. 36 mental health care institutes that were in contact with medical centers from Amsterdam, Groningen, Maastricht and Utrecht in the Netherlands, as well as from the Dutch-speaking part of Belgium participated. Inclusion criteria for the patients were a good command of the Dutch language, being able and willing to give informed consent and a diagnosis of a non-affective psychotic disorder (DSM-IV) (American Psychiatric Association, Washington, 1994). A diagnosis of SSD was established using DSM-IV criteria, assessed with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992) or the Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1; Wing et al., 1990). A diagnosis of SSD included DSM-IV diagnostic codes: schizophrenia disorganized type 295.10 (n = 15; 3.3%), schizophrenia paranoid type 295.30 (n = 268; 59.7%), schizophreniform disorder 295.40 (n = 4; 0.9%), schizoaffective disorder 295.70 (n = 68; 15.1%), schizophrenia undifferentiated type 295.90 (n = 23; 5.2%), psychotic disorder NOS 298.9 (n = 71; 15.8%).

NESDA is a naturalistic, prospective cohort study, consisting of 2981 participants aged 18–65 years, including 1115 persons with a current (six-month recency) diagnosis of depression and/or anxiety disorder, assessed by the CIDI (World Health Organisation, 1990), 907 persons with lifetime diagnoses of depression and/or anxiety disorders or at risk because of family history or subthreshold depressive or anxiety symptoms, and 652 healthy controls, defined as the absence of lifetime psychopathology. Participants were recruited from primary care practices and specialized mental health institutions in the regions of Amsterdam, Leiden, Groningen, Drenthe and Friesland in The Netherlands. To reflect different stages and settings in psychopathology, participants were recruited from different places: 19% came from the community, 27% from specialized mental health-care settings and 54% from the primary care. Inclusion criteria were age between 18 and 65 years. Exclusion criteria were an insufficient command of the Dutch language and a primary clinical diagnosis of other psychiatric conditions.

For the current study, data were collected from the second assessment of GROUP (n = 1953) in which the QIDS-SR (Rush et al., 2003) instrument was assessed for the first time, and from the first assessment of NESDA (n = 2981). For comparisment of severity of depression, healthy controls were derived from NESDA (n = 652). Patients from GROUP (n = 1129) and NESDA (n = 1925) were selected, if they had filled in the QIDS-SR with no more than 3 items missing. To avoid selection bias due to differences in age range between both cohorts (GROUP 16–50 years and NESDA 18–65 years), only patients with an age between 18 and 50 years old were included. Because we wanted to investigate depressive symptomatology in non-remitted psychotic patients, patients with current symptomatology within the last 6 months were selected and, hence, patients in remission were excluded from both samples. In GROUP, remission of psychotic symptoms at the time of assessment was determined following remission criteria as proposed by the Remission in Schizophrenia Working Group (Andreasen et al., 2005): remission was defined as a score of 3 (mild) or less, on eight PANSS items and remission had to be stable for at least 6 months based

on interview and medical records. In NESDA, the CIDI (World Health Organisation, 1990) was used to assess if patients had a major depressive disorder in the last 6 months. Three groups were identified, including healthy controls (n = 417), current MDD (n = 816) and current SSD (n = 449) (see Fig. 1).

2.2. Measures

2.2.1. Depressive symptoms

In both GROUP and NESDA, the severity of depressive symptoms was measured with the QIDS-SR, which consists of 16 questions, assessing the severity of nine DSM-IV-diagnostic symptoms of depression (1 sad mood; 2 concentration; 3 problematic view of the self; 4 suicidal ideation; 5 interest; 6 energy/fatigue; 7 sleep disturbance (initial, middle, and late insomnia or hypersomnia); 8 decrease or increase in appetite or weight; 9 psychomotor agitation or retardation). The total severity score ranges from 0 to 27. In previous studies it was feasible to identify different depressive symptom domains within the QIDS-SR. Therefore, in accordance with these findings (Schaakxs et al., 2017; Wardenaar et al., 2010), we defined a mood/cognition domain (including 5 QIDS-SR items) and a somatic/vegetative domain (including 11 QIDS-SR items).

To explore differences in depressive profiles on item level, all 16 QIDS-SR items were dichotomized (present versus absent), with a score of 0 indicating absence of the symptom during the last 7 days, in accordance to previous publications (Khan et al., 2006; Schaakxs et al., 2017). The initial scores for having a problem (1,2 or 3) were converted to 1 indicating presence of a symptom.

2.2.2. Sociodemographic and clinical characteristics

For comparisons across persons with SSD, MDD and healthy controls, age, gender, years of education and medication use were assessed. Medication use was defined as current use of antidepressants, antipsychotic medication or benzodiazepines. In GROUP, information about medication use and adherence was derived from interviewing the patient, information from medical files and from caregivers. The name of prescribed medication, mean dosage taken and the current use status were registered. In NESDA, medication use in the prior month was registered by observation of the medication container that was brought in.

Additional clinical characteristics, that showed predictive value in previous research (Upthegrove et al., 2017) and were available in

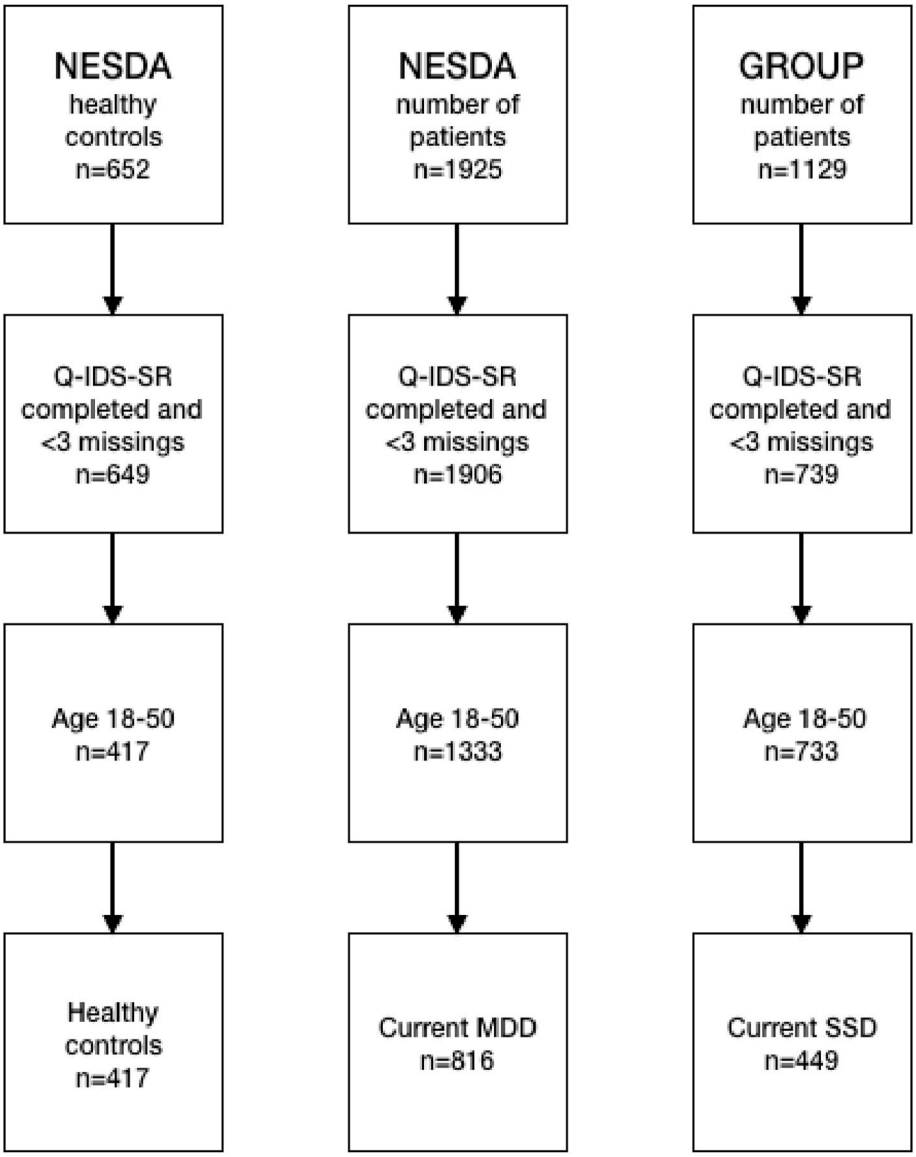

Fig. 1. Flow-chart of the selection procedure of the study sample.

GROUP, were selected in the SSD cohort. These included psychotic symptomatology, duration of illness, number of psychotic episodes, age of onset, cannabis use, alcohol use, and current somatic treatment. In addition, social functioning characteristics were selected, including social functioning, current household, and the global assessment of functioning. For the assessment of severity of psychotic symptomatology, the Positive and Negative Syndrome Scale was used (PANSS; Kay et al., 1987). The PANSS is a 30-item scale, with 7 positive items, 7 negative items and 16 general items. Items are rated on a scale from 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210. For the current study, the PANSS subscale scores for positive, negative and general symptoms were analysed. The duration of illness in years was determined from the first contact with a mental health care institution and was based on self-report and information derived from family and medical records. The mean number of psychotic episodes was calculated by counting the cumulative (first and second assessment of GROUP) number of psychotic episodes. Age of onset was defined as the age of first psychosis and based on self-report and information derived from medical records. The use of cannabis or alcohol was assessed by the Composite International Diagnostic Interview (World Health Organisation, 1990); for the current study, no use, abuse, or dependence was dichotomized as no lifetime misuse or dependence; alcohol use was assessed in the CIDI interview as the number of units a week. Current somatic treatment was defined as current treatment (yes or no) for any somatic disease and based on self-report by the respondent. Social functioning was scored using the Social Functioning Scale (SFS; Birchwood et al., 1990); current household situation was assessed by self-report and defined as independent (living alone) or dependent (living with parents, sheltered, or living with others); global functioning was assessed using the Global Assessment of Functioning (GAF) disabilities score (American Psychiatric Association, 2000).

2.3. Statistical analysis

First, descriptive data analyses were performed to describe the study population. Baseline characteristics across the three groups (healthy controls, SSD and MDD) were compared using two-tailed chi-square tests for categorical variables, one-way analysis of variance statistics (ANOVA) for continuous variables, and the non-parametric Kruskal-Wallis test for non-normally distributed variables. Second, using analysis of co-variance (ANCOVA), the severity of QIDS-SR total score, and the sub-scores for mood/cognition and somatic/vegetative domains were compared across healthy controls, SSD and MDD. ANCOVA analyses were adjusted for age, gender and years of education. For effect size comparison of depressive symptom domains between patient groups, Cohen's d scores were calculated.

Third, to be able to study the relative distribution of depressive symptoms between SSD and MDD, taking the initial higher severity of these symptoms in MDD into account, the distribution of all 16 individual QIDS-SR items (dichotomized) between SSD and MDD was presented using odds ratios (OR) and 95% confidence intervals (CI) using logistic regression analysis. The regression analyses were adjusted for age, gender, and years of education. Because we expected the severity of depressive symptoms to be highest in MDD and since we wanted to examine whether there are specific symptoms standing out in the overall symptom comparison between MDD and SSD, analyses were additionally adjusted for total QIDS-SR scores.

Fourth, in the subpopulation of SSD patients ($n = 449$), linear regression analysis was used to identify predictors of higher total depression scores, and higher scores on the mood/cognition and somatic/vegetative symptom domains. Different variables were entered one by one in separate, unadjusted analyses with total QIDS-SR score, mood/cognition or somatic/vegetative symptom domains as dependent variables. All predictors that were significantly ($p < 0.05$) associated with higher depression severity in unadjusted analyses were considered putative confounders, and, hence, entered in final separate multivariable (stepwise) regression models for QIDS-SR total score, for mood/cognition symptom domain and for somatic/vegetative symptom domain (Table 3). Multivariable analyses were adjusted for age, gender and years of education. Multicollinearity was tested using variance inflation factor (VIF). In case of multicollinearity (VIF>3) predictor variables were left out of the analysis. Therefore, the PANSS general subscale score and the GAF score were left out of the analysis.

Release number 7.0 of the GROUP database was used for the present analyses. Analyses were conducted with SPSS 24 (IBM SPSS Statistics).

3. Results

Table 1 presents the sample characteristics and group comparisons for all outcome variables. Bivariate analyses showed that mean age differed significantly across healthy controls, SSD and MDD patients, with the highest age in MDD (mean 35.7 (SD 9.1)) and lowest in SSD (mean 30.8 (SD 7.0)). Males were overrepresented in the SSD group, and underrepresented in healthy controls and in MDD patients. Healthy controls had the most years of education. According to interpretation guidelines (ids-qids.org (Rush et al., 2003)), of the 449 SSD patients, 60.4% showed clinically relevant severity of depression (QIDS-SR score ≥ 6).

Mean total QIDS-SR scores, mood/cognition domain score and somatic/vegetative domain score all significantly differed between groups, with highest scores in MDD, followed by SSD and lowest in healthy controls. Fig. 2 shows the mean mood/cognition and somatic/vegetative depression domain scores across SSD and MDD. For the mood/cognition domain, effect size between SSD and MDD was large ($d = 1.13$), whereas the effect size between SSD and MDD for the somatic/vegetative domain was smaller ($d = 0.74$).

Fig. 3 shows all 16 (dichotomized) QIDS-SR items, and their relative associations with SSD and MDD, adjusted for age, gender, education and total QIDS-SR severity. Of the 16 individual QIDS-SR items, 7 items (whereof 6 somatic/vegetative items) were not differentially present in SSD versus MDD. Of the remaining 9 items, 1 somatic/vegetative item ("Sleeping too much") was relatively more common in SSD patients, and 8 items (whereof 4 mood/cognition domain items and 4 somatic/vegetative items) were relatively more common in MDD patients as compared to SSD patients. Post-hoc analyses, with additional adjustment for medication use, did not alter these findings (data not shown).

Table 2 shows the characteristics of SSD patients, and associations between socio-demographic, clinical, and social functioning characteristics with depression severity for the 449 SSD patients using regression analysis. These data illustrate that respondents were, in general, not in their early stage of SSD. Next, fewer years of education were significantly associated with higher total QIDS-SR score. Antidepressants use was significantly associated with higher overall severity of depression (including total QIDS-SR score, mood/cognition and somatic/vegetative symptom domain scores), antipsychotic and benzodiazepine use were only associated with somatic/vegetative symptoms. More positive and general symptomatology on the PANSS was significantly associated with higher overall depression severity; with highest regression coefficients found for the PANSS general subscale score. Negative symptoms were only significantly associated with QIDS-SR total score. Lower social functioning and lower global functioning were significantly associated with higher overall depression severity. Univariate regression analyses were al corrected for multiple comparisons (Bonferroni correction).

In multivariable regression analyses (Table 3), lower social functioning, male gender, the use of benzodiazepine and higher scores of the PANSS positive symptom scale remained significantly associated with higher overall severity of depression. Lower social functioning, benzodiazepine use and male gender were associated with mood/cognition symptoms, in fully adjusted models. Finally, lower social functioning, male gender, higher scores of the PANSS positive symptom scale and medication use (benzodiazepine, antipsychotic and antidepressants) were associated with somatic/vegetative symptoms in fully adjusted

Table 1
Bivariate comparison of subjects according to diagnosis.

			healthy control	current SSD	current MDD	Statistics	overall
			n = 417	n = 449	n = 816		p-value
Age mean (SD) years		n = 1682	32.2 (10.1)	30.8 (7.0)	35.7 (9.1)	A,B,C	<0.001
Gender male (%)		n = 1682	151 (36.2)	349 (77.7)	245 (30.0)	A,B,C	<0.001
Education mean (SD) years		n = 1682	13.1 (3.0)	11.2 (2.8)	11.7 (3.2)	A,B	<0.001
Medication use (%)	antidepressant use	n = 1682	3 (0.7)	78 (17.4)	353 (43.3)	A,B,C	<0.001
	antipsychotic use	n = 1682	0 (0.0)	355 (79.1)	29 (3.6)	A,B,C	<0.001
	benzodiazepine use	n = 1682	1 (0.2)	83 (18.5)	96 (11.8)	A,B,C	<0.001
Total score QIDS-SR (0–27) mean (SD)		n = 1682	3.4 (3.1)	7.6 (5.0)	12.7 (5.0)	A,B,C	<0.001
Mood cognition symptom scale (0–5) mean (SD)		n = 1682	0.76 (1.2)	2.1 (1.7)	3.7 (1.3)	A,B,C	<0.001
Somatic vegetative symptom scale (0–9) mean (SD)		n = 1682	2.1 (1.7)	4.0 (2.0)	5.6 (1.9)	A,B,C	<0.001
Mood/cognitive symptom domain							
Feeling depressed (%)		n = 1681	97 (23.3)	252 (56.3)	719 (88.1)	A,B,C	<0.001
Less general interest (%)		n = 1676	39 (9.4)	152 (34.2)	592 (72.6)	A,B,C	<0.001
Problems with concentration (%)		n = 1678	101 (24.2)	235 (52.5)	709 (87.2)	A,B,C	<0.001
Problematic view of the self (%)		n = 1666	57 (13.7)	179 (40.0)	621 (77.3)	A,B,C	<0.001
Thoughts of death and suicide (%)		n = 1673	21 (5.0)	113 (25.3)	388 (47.9)	A,B,C	<0.001
Somatic/vegetative symptom domain							
Problems falling asleep (%)		n = 1679	101 (24.3)	246 (54.9)	481 (59.0)	A,B	<0.001
Waking up during the night (%)		n = 1679	184 (44.2)	205 (45.7)	621 (76.3)	B,C	<0.001
Waking up too early (%)		n = 1670	54 (12.9)	114 (25.5)	285 (35.4)	A,B,C	<0.001
Sleeping too much (%)		n = 1677	126 (30.2)	319 (71.0)	394 (48.6)	A,B,C	<0.001
Change in appetite (%)	no change in appetite	n = 1669	338 (81.1)	251 (55.9)	242 (29.7)	A,B,C	<0.001
	less appetite		46 (11.0)	74 (16.8)	300 (37.0)		
	more appetite		33 (8.9)	116 (25.8)	269 (33.0)		
Weight changes (%)	no weight changes	n = 1667	273 (65.5)	231 (51.4)	292 (35.5)	A,B,C	<0.001
	weight loss		69 (16.5)	103 (22.9)	236 (44.7)		
	weight gain		75 (18.0)	106 (23.6)	282 (34.6)		
Less energy (%)		n = 1679	108 (25.9)	218 (48.9)	699 (85.7)	A,B,C	<0.001
Feeling restless (%)		n = 1675	67 (16.1)	157 (35.1)	535 (66.0)	A,B,C	<0.001
Feeling slowed down (%)		n = 1679	22 (5.3)	128 (28.5)	430 (52.7)	A,B,C	<0.001

SSD = schizophrenia spectrum disorder; MDD = major depressive disorder; QIDS-SR = quick inventory of depression symptomatology self-report. Total QIDS-SR score range from 0 to 27, mood/cognition score range from 0 to 5 and somatic/vegetative score range from 0 to 9. A represents a significant difference between healthy controls and current SSD patients, B between healthy controls and current MDD and C between current SSD and current MDD.

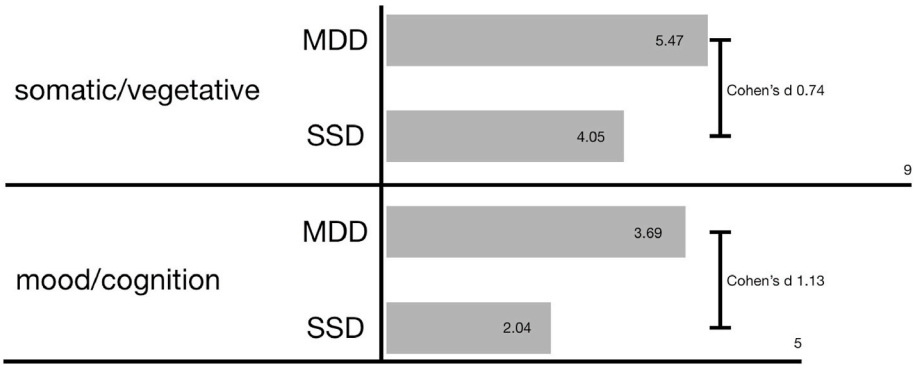

Fig. 2. Mean scores of QIDS-SR total score, somatic/vegetative and mood/cognition symptom domain scores for the two patient groups compared with healthy controls. Total QIDS-SR score range from 0 to 27, somatic/vegetative symptom domain score 0–9, and mood/cognition symptom domain score 0–5. Between patient groups within QIDS-SR total score, somatic/vegetative and mood/cognition symptom domains effect sizes (Cohen's d) are shown. Adjusted for age, gender and years of education.

models.

4. Discussion

The current study investigated the severity of depressive symptoms and explored depressive symptom profiles in persons with SSD, MDD and healthy controls, using the QIDS-SR. We found that more than half (60.4%) of the SSD patients reported clinically relevant depressive symptoms. A mood/cognition profile was more prominent in MDD compared to SSD. Comparisons between the two groups on QIDS-SR items, adjusted for depression severity, revealed similarities in the depressive symptom profile between SSD and MDD for somatic/vegetative items (except for sleeping too much). Analyses within the SSD patient sample showed worse social functioning to be most substantially associated with severity of depressive symptoms, next to male gender and medication use, especially benzodiazepines. Likewise, severity of positive symptoms was associated with more severe depressive symptoms. Antidepressant or antipsychotic use was associated with more severe somatic/vegetative symptoms.

Our finding that 60.4% of SSD patients experienced clinically relevant depressive symptoms (QIDS-SR score ≥6) lies within the previously reported prevalence range of 6–65% (Siris and Bench, 2003), but is higher than the 43.9% prevalence rate in the recent systematic review and meta-analysis by Herniman et al. (2019), and prevalence rates of 47.5% found in SSD patients older than 55 years (Hoertel et al., 2019). This illustrates the large variation in distribution of depressive symptoms in SSD (Siri and Bench, 2003), partly due to different instruments applied. A previous GROUP study, which investigated depression with the Calgary Depression Scale for Schizophrenia (CDSS) and the QIDS-SR, reported clinical depression measured with the CDSS to be present in only 17% of patients (Lako et al., 2014). However, this study also included remitted SSD patients resulting in lower mean QIDS-SR scores of 6.6 (SD = 4.9).

Severity of both depressive symptom domains was highest in MDD

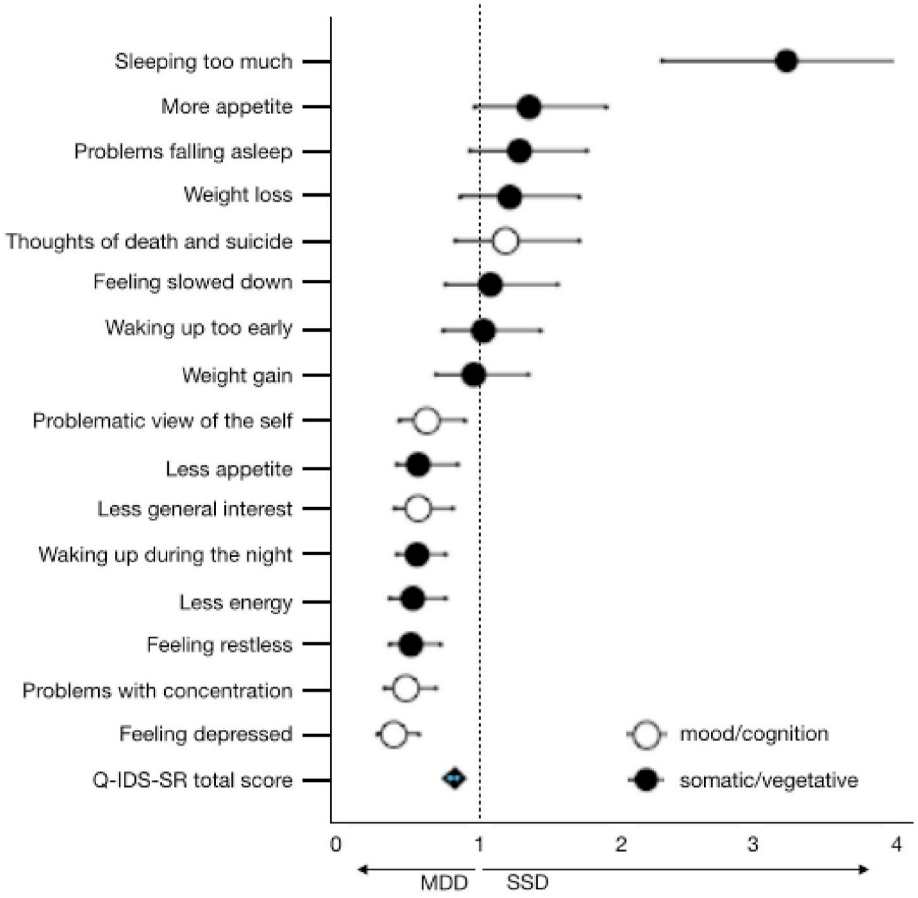

Fig. 3. Odds ratio (OR) and 95% confidence intervals (CI) for the relative association between a diagnosis of major depressive disorder (MDD) and schizophrenia spectrum disorder (SSD) and all 16 QIDS-SR items. OR<1 indicates symptom is relatively more strongly associated with a diagnosis of MDD, OR>1 indicates symptom is relatively more strongly associated with diagnosis of SSD. Adjusted for age, gender, years of education and QIDS-SR total score.

Table 2
Characteristics and prediction of depressive severity in the current schizophrenia spectrum disorder population (N = 449).

		Characteristics	QIDS-SR total		Mood/cognition		Somatic/vegetative	
			Beta (SE B)	p-value	Beta (SE B)	p-value	Beta (SE B)	p-value
Demographic data								
Age mean (SD) years		30.8 (10.1)	−0.02 (0.03)	0.63	−0.03 (0.01)	0.52	−0.004 (0.01)	0.94
Gender male (%)		349 (77.7)	0.08 (0.57)	0.10	0.05 (0.19)	0.29	0.12 (0.23)	0.01
Education mean (SD) years		11.2 (2.8)	−0.17 (0.09)	**<0.001**	−0.13 (0.03)	0.01	−0.12 (0.03)	0.14
Clinical data								
Medication use (%)	antidepressant use	78 (17.4)	0.17 (0.62)	**<0.001**	0.18 (0.21)	**<0.001**	0.15 (0.25)	**0.001**
	antipsychotic use	355 (79.1)	0.11 (0.58)	0.03	0.07 (0.19)	0.15	0.16 (0.23)	**0.001**
	benzodiazepine use	83 (18.5)	0.13 (0.61)	0.01	0.12 (0.20)	0.01	0.17 (0.24)	**<0.001**
PANSS positive symptom subscale		1.8 (0.7)	0.22 (0.33)	**<0.001**	0.16 (0.11)	**0.001**	0.19 (0.13)	**<0.001**
PANSS negative symptom subscale		1.9 (0.8)	0.17(0.30)	**<0.001**	0.13 (0.10)	0.01	0.10 (0.12)	0.03
PANSS general symptom subscale		1.6 (0.5)	0.33 (0.49)	**<0.001**	0.28 (0.16)	**<0.001**	0.24 (0.20)	**<0.001**
Duration of illness mean (SD) years		8.8 (4.5)	−0.001 (0.05)	0.98	−0.02 (0.02)	0.66	−0.01 (0.02)	0.92
Number of psychotic episodes mean (SD)		1.8 (1.1)	0.07 (0.16)	0.14	0.06 (0.05)	0.24	0.10 (0.06)	0.03
Age of onset (SD) years		22.2 (6.3)	−0.02 (−0.04)	0.62	−0.01 (0.01)	0.77	0.001 (0.02)	0.99
Cannabis misuse (%)		56 (12.5)	−0.003 (0.72)	0.96	0.06 (0.24)	0.24	0.02 (0.29)	0.61
Alcohol use mean (SD) units a week		6.6 (12.5)	−0.02 (0.02)	0.62	0.001 (0.01)	0.98	0.002 (0.01)	0.96
Current somatic treatment		240 (53.5)	0.04 (0.50)	0.48	0.02 (0.17)	0.66	0.05 (0.20)	0.30
Social data								
Social functioning scale score mean		110.2 (9.3)	−0.44 (0.02)	**<0.001**	−0.39 (0.01)	**<0.001**	−0.26 (0.01)	**<0.001**
Current household		168 (37.4)	0.07 (0.50)	0.15	0.05 (0.17)	0.48	0.03 (0.20)	0.04
GAF-score disabilities mean (SD)		55.5 (14.9)	−0.27 (0.02)	**<0.001**	−0.19 (0.01)	**<0.001**	−0.23 (0.01)	**<0.001**

Data of age, gender, education and medication use in characteristics column are the same data as in Table 1. In bold, p-values reaching statistical significance level of $p < 0.003$ after Bonferroni correction. (SD) Standard deviation. PANSS positive and negative syndrome scale, GAF global assessment of functioning.

Table 3
Multivariable analyses of variables that were associated with depression severity after stepwise introduction in regression analysis.

TOTAL CURRENT SSD n = 449		
	Beta (SE B)	p-value
	QIDS-SR total score	
Social functioning scale score mean	−0.43 (0.02)	**<0.001**
Gender male	0.18 (0.53)	**<0.001**
Medication use Benzodiazepine	0.14 (0.56)	**0.002**
PANSS positive symptom subscale	0.12 (0.33)	**0.008**
	Mood/cognition	
Social functioning scale score mean	−0.40 (0.01)	**<0.001**
Medication use Benzodiazepine	0.16 (0.20)	**0.001**
Gender male	0.12 (0.19)	**0.008**
	Somatic/vegetative	
Social functioning scale score mean	−0.19 (0.01)	**<0.001**
Medication use Benzodiazepine	0.16 (0.24)	**0.001**
Gender male	0.16 (0.23)	**0.001**
PANSS positive symptom subscale	0.16 (0.14)	**0.001**
Medication use Antipsychotics	0.13 (0.24)	**0.007**
Medication use Antidepressives	0.10 (0.25)	**0.042**

Variables for each domain shown in order of highest regression coefficient. SSD schizophrenia spectrum disorder, PANSS positive and negative syndrome scale.

patients, although we found a difference in the distribution of both domains between SSD and MDD. For the mood/cognition domain, large differences were found between SSD and MDD patients with 4 out of 5 mood/cognition symptoms (e.g. feeling depressed) relatively more common in MDD. This is in line with findings of Häfner et al. (2005b) and Rahim and Rashid (2017), who found symptoms of depressed mood, loss of interest, and guilty thoughts to be more severe in patients with a primary diagnosis of depression compared to patients with a primary psychotic disorder.

In contrast to these differences, a smaller effect size was found for differences in the somatic/vegetative symptom domain. Further exploration on item level showed that presence of 6 out of 11 somatic/vegetative symptoms was not significantly different between SSD and MDD. This again is in line with findings of Rahim and Rashid (2017), who found somatic/vegetative symptoms (appetite and sleep disturbances) to be the most important depressive symptoms within SSD. Also, Häfner et al. (2005b) found disturbed appetite and/or sleep to be one of two most prevalent depressive symptoms in patients with a primary psychotic disorder, with a non-significant difference compared with primary depressive patients. We found the symptom of 'sleeping too much' to be relatively more common in SSD patients than in MDD patients. This could well be a reflection of negative symptoms as part of the SSD symptom spectrum or also related to common side-effects of the antipsychotic medication.

Previous findings in MDD research indicated that somatic/vegetative symptoms may be linked to alterations in somatic parameters and metabolic (Lamers et al., 2018; Penninx, 2017) or cardiovascular syndromes (De Miranda Azevedo et al., 2014; Roest et al., 2011). This may account for SSD patients as well. Higher prevalence rates of these metabolic and cardiovascular syndromes, as previously demonstrated in SSD (Howell et al., 2019; Mitchell et al., 2013), may be associated with high levels of somatic/vegetative symptoms in SSD. Indeed, in both SSD and MDD research, somatic/vegetative symptoms as weight, food-intake and sleep changes have been linked to inflammatory or immunopathology processes (Kucerova et al., 2015; Lee et al., 2017), and in both SSD and MDD research, multiple lines of evidence are pointing to involvement of inflammation and autoimmune processes in the aetiopathogenesis (Khandaker et al., 2017; Kroken et al., 2019; Penninx and Lange, 2018). Therefore, somatic/vegetative symptoms provide a possible link between inflammation and autoimmune processes and metabolic and cardiovascular consequences in both MDD and SSD.

Finally, in the subsample of 449 current SSD patients, we examined which factors were associated with overall QIDS-SR scores and somatic/vegetative or mood/cognition symptom domains specifically. Social functioning showed the strongest association with higher overall depression severity. The same pattern was seen in a report of Schennach and colleagues, who found PANSS general items of social withdrawal and avoidance to be associated with depression items (Schennach et al., 2015). In a report of Harvey and colleagues (2017), the group with highest self-reported depression had significant poorer social functioning. Baynes et al. (2000) showed that persistent depressive symptoms were related to the patient's perception of social support. Male gender predicted higher severity of overall depressive symptoms in adjusted analysis, which is in line with the findings of Herniman et al. (2019), but in contrast with previous findings in a review of Abel and colleagues (Abel et al., 2010). The use of medication, and especially benzodiazepine, was associated with higher overall depressive symptomatology, which could be an effect of the subscription of this co-medication in case of more severe psychopathology. The association between the use of antipsychotic or antidepressant medication and more severe somatic/vegetative symptom domain score could well be an effect of the propensity of these medications to cause metabolic disturbances like weight gain, and appetite disturbances (Balt et al., 2011; Casey et al., 2004). We found an association between higher PANSS positive subscale score and total QIDS-SR score, which is in line with previous findings (Drake et al., 2004; Müller et al., 2001; Schennach et al., 2015), although some researchers reported only associations with negative symptoms (Lançon et al., 2001; Majadas et al., 2012). The association between positive symptom and depressive symptom domains can be interpreted as an illustration that positive and depressive symptoms co-occur during acute stages/relapses (Birchwood et al., 2005; Häfner et al., 2005a). These findings should be cautiously interpreted since reversed causality cannot be excluded.

We should also acknowledge the following limitations. The SSD and MDD patient groups were not equal on social demographics, partly reflecting real difference in prevalence (e.g. SSD is more often present in males, MDD in females). Next, due to different methods of initial data collection in both GROUP and NESDA, only a limited number of clinical and social data could be compared between all three samples. Moreover, current findings may not apply for patients with severe SSD since GROUP participants represent a relatively high functioning sample of SSD patients. In previous research conducted in the GROUP cohort, the QIDS-SR showed weak correlations with negative symptom ratings of the PANSS, although some QIDS-SR items showed overlap with negative symptoms (concentration difficulties and lack of interest) (Lako et al., 2014). Therefore, reported problems with concentration and lack of interest in the SSD sample cannot clearly be defined as symptoms of depression, but might be part of experienced negative symptoms. However, overall, Lako et al. (2014) concluded that the QIDS-SR discriminated depressive symptoms from negative symptoms in an acceptable way, which is in line with a previous publication (Simonsen et al., 2010). In order to be able to compare findings between SSD and MDD, and based on availability on both cohorts, we used the QIDS-SR instead of the CDSS, seen as the golden standard for assessment of core depressive symptoms in SSD (Schennach et al., 2012). The QIDS-SR showed moderate overall agreement with the CDSS, suggesting conceptual differences between these two instruments (Lako et al., 2014). Especially, the QIDS-SR depressive symptoms concerning 'sleep' and 'appetite' showed low agreement with the CDSS. Therefore, our findings should be seen as explorative because uncertainty remains about the validity of the QIDS-SR in identifying depressive symptom domains in SSD. Finally, due to the observational nature of the study and cross-sectional investigations, no causal conclusions can be drawn from the presented findings.

In sum, depressive symptoms are an important part of the SSD symptom profile. Social functioning, medication use and psychopathology are associated with depressive symptomatology in SSD. The depressive symptom profile found in current SSD patients showed similarities with the symptom profile of MDD patients especially in the

somatic/vegetative symptom domain. Therefore, aetiopathogenetic pathways found in MDD research concerning somatic/vegetative symptoms could well be playing a similar role in SSD, and should therefore be a focus of future research.

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Declaration of competing interest

None.

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References

Abel, K.M., Drake, R., Goldstein, J.M., 2010. Sex differences in schizophrenia. Int. Rev. Psychiatr. 22, 417–428. https://doi.org/10.3109/09540261.2010.515205.

American Psychiatric Association, Washington, D., 1994. Diagnostic and statistical manual of mental disorders fourth ed.

American Psychiatric Association, 2000. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. American Psychiatric Association, Washington DC. Text Revision.

Andreasen, N.C., Carpenter, W.T., Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D. R., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. Am. J. Psychiatr. 162, 441–449. https://doi.org/10.1176/appi.ajp.162.3.441.

Andreasen, N.C., Flaum, M., Arndt, S., 1992. Comprehensive assessment of symptoms and history (CASH) assessing diagnosis and psychopathology. Arch. Gen. Psychiatr. 49, 615–623.

Balt, S.L., Galloway, G.P., Baggott, M.J., Schwartz, Z., Mendelson, J., 2011. Mechanisms and genetics of antipsychotic-associated weight gain. Clin. Pharmacol. Ther. 90, 179–183. https://doi.org/10.1038/clpt.2011.97.

Baynes, D., Mulholland, C., Cooper, S.J., Montgomery, R.C., MacFlynn, G., Lynch, G., Kelly, C., King, D.J., 2000. Depressive symptoms in stable chronic schizophrenia: prevalence and relationship to psychopathology and treatment. Schizophr. Res. 45, 47–56. https://doi.org/10.1016/S0920-9964(99)00205-4.

Birchwood, M., Iqbal, Z., Upthegrove, R., 2005. Psychological pathways to depression in schizophrenia: studies in acute psychosis, post psychotic depression and auditory hallucinations. Eur. Arch. Psychiatr. Clin. Neurosci. 255, 202–212. https://doi.org/10.1007/s00406-005-0588-4.

Birchwood, M., Smith, J., Cochrane, R., Wetton, S., Copestake, S., 1990. The social functioning scale the development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. Br. J. Psychiatry 157, 853–859. https://doi.org/10.1192/bjp.157.6.853.

Casey, D.E., Haupt, D.W., Newcomer, J.W., Henderson, D.C., Sernyak, M.J., Davidson, M., Lindenmayer, J.-P., Manoukian, S.V., Mary, F.A.C.C., Banerji, A., Lebovitz, H.E., Hennekens, C.H., 2004. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia table 1. "The Metabolic Syndrome" According to the Adult Treatment Panel III a. J Clin Psychiatry 65.

Cavelti, M., Beck, E.M., Kvrgic, S., Kossowsky, J., Vauth, R., 2012. The role of subjective illness beliefs and attitude toward recovery within the relationship of insight and depressive symptoms among people with schizophrenia spectrum disorders. J. Clin. Psychol. 68, 462–476. https://doi.org/10.1002/jclp.20872.

Chan, M.-S., Chung, K.-F., Yung, K.-P., Yeung, W.-F., 2017. Sleep in schizophrenia: a systematic review and meta-analysis of polysomnographic findings in case-control studies. Sleep Med. Rev. 32, 69–84. https://doi.org/10.1016/j.smrv.2016.03.001.

Conley, R.R., Ascher-Svanum, H., Zhu, B., Faries, D.E., Kinon, B.J., 2007. The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. Schizophr. Res. 90, 186–197. https://doi.org/10.1016/j.schres.2006.09.027.

Cotton, S.M., Lambert, M., Schimmelmann, B.G., Mackinnon, A., Gleeson, J.F.M., Berk, M., Hides, L., Chanen, A., McGorry, P.D., Conus, P., 2012. Depressive symptoms in first episode schizophrenia spectrum disorder. Schizophr. Res. 134, 20–26. https://doi.org/10.1016/j.schres.2011.08.018.

De Haan, L., Lavalaye, J., Linszen, D., Dingemans, P.M.A.J., Booij, J., 2000. Subjective experience and striatal dopamine D 2 receptor occupancy in patients with schizophrenia stabilized by olanzapine or risperidone. Am. J. Psychiatr. 157, 1019–1020. https://doi.org/10.1176/appi.ajp.157.6.1019.

De Haan, L., Van Bruggen, M., Lavalaye, J., Booij, J., Dingemans, P.M.A.J., Linszen, D., 2003. Subjective experience and D 2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. Am. J. Psychiatr. 160, 303–309. https://doi.org/10.1176/appi.ajp.160.2.303.

De Miranda Azevedo, R., Roest, A.M., Hoen, P.W., De Jonge, P., 2014. Cognitive/affective and somatic/affective symptoms of depression in patients with heart disease and their association with cardiovascular prognosis: a meta-analysis. Psychol. Med. 44 (13), 2689–2703. https://doi.org/10.1017/S0033291714000063.

Dollfus, S., Ribeyre, J.M., Petit, M., 2000. Objective and subjective extrapyramidal side effects in schizophrenia: their relationships with negative and depressive symptoms. Psychopathology 33, 125–130. https://doi.org/10.1159/000029133.

Drake, R.J., Pickles, A., Bentall, R.P., Kinderman, P., Haddoc, G., Tarrier, N., Lewis, S.W., 2004. The evolution of insight, paranoia and depression during early schizophrenia. Psychol. Med. 285–292. https://doi.org/10.1017/S0033291703008821.

Emsley, R.A., Oosthuizen, P.P., Joubert, A.F., Roberts, M.C., Stein, D.J., 1999. Depressive and anxiety symptoms in patients with schizophrenia and schizophreniform disorder. J. Clin. Psychiatr. 60, 747–751.

Fond, G., Boyer, L., Berna, F., Godin, O., Bulzacka, E., Andrianarisoa, M., Brunel, L., Aouizerate, B., Capdevielle, D., Chereau, I., Coulon, N., D'Amato, T., Dubertret, C., Dubreucq, J., Faget, C., Leignier, S., Lançon, C., Mallet, J., Misdrahi, D., Passerieux, C., Rey, R., Schandrin, A., Urbach, M., Vidailhet, P., Leboyer, M., Schürhoff, F., Llorca, P.-M., 2018. Remission of depression in patients with schizophrenia and comorbid major depressive disorder: results from the FACE-SZ cohort. Br. J. Psychiatry 1–7. https://doi.org/10.1192/bjp.2018.87.

Gregory, A., Mallikarjun, P., Upthegrove, R., 2017. Treatment of depression in schizophrenia: systematic review and meta-analysis. Br. J. Psychiatry 211, 198–204. https://doi.org/10.1192/bjp.bp.116.190520.

Häfner, H., Maurer, K., Trendler, G., An Der Heiden, W., Schmidt, M., 2005a. The early course of schizophrenia and depression. Eur. Arch. Psychiatr. Clin. Neurosci. 255, 167–173. https://doi.org/10.1007/s00406-005-0584-8.

Häfner, H., Maurer, K., Trendler, G., An Der Heiden, W., Schmidt, M., Könnecke, R., 2005b. Schizophrenia and depression: challenging the paradigm of two separate diseases - a controlled study of schizophrenia, depression and healthy controls. Schizophr. Res. 77, 11–24. https://doi.org/10.1016/j.schres.2005.01.004.

Hawton, K., Sutton, L., Haw, C., Sinclair, J., Deeks, J.J., 2005. Schizophrenia and suicide: systematic review of risk factors. Br. J. Psychiatry 187, 9–20. https://doi.org/10.1192/bjp.187.1.9.

Henderson, D.C., Vincenzi, B., Andrea, N.V., Ulloa, M., Copeland, P.M., 2015. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. The lancet. Psychiatry 2, 452–464. https://doi.org/10.1016/S2215-0366(15)00115-7.

Herniman, S.E., Allott, K., Phillips, L.J., Wood, S.J., Uren, J., Mallawaarachchi, S.R., Cotton, S.M., 2019. Depressive psychopathology in first-episode schizophrenia spectrum disorders : a systematic review, meta-analysis and meta-regression. Psychol. Med. 49 (15), 2463–2474.

Hoertel, N., Jaffré, C., Pascal de Raykeer, R., McMahon, K., Barrière, S., Blumenstock, Y., Portefaix, C., Raucher-Chéné, D., Béra-Potelle, C., Cuervo-Lombard, C., Chevance, A., Guerin-Langlois, C., Lemogne, C., Airagnes, G., Peyre, H., Kaladjian, A., Limosin, F., 2019. Subsyndromal and syndromal depressive symptoms among older adults with schizophrenia spectrum disorder: prevalence and associated factors in a multicenter study. J. Affect. Disord. 251, 60–70. https://doi.org/10.1016/j.jad.2019.03.007.

Hoffmann, A., Sportelli, V., Ziller, M., Spengler, D., 2017. Epigenomics of major depressive disorders and schizophrenia: early life decides. Int. J. Mol. Sci. 18, 1–25. https://doi.org/10.3390/ijms18081711.

Hou, C.L., Ma, X.R., Cai, M.Y., Li, Y., Zang, Y., Jia, F.J., Lin, Y.Q., Chiu, H.F.K., Ungvari, G.S., Hall, B.J., Zhong, B.L., Cao, X.L., Xiang, Y.T., 2016. Comorbid moderate–severe depressive symptoms and their association with quality of life in Chinese patients with schizophrenia treated in primary care. Community Ment. Health J. 52, 921–926. https://doi.org/10.1007/s10597-016-0023-5.

Howell, S., Yarovova, E., Khwanda, A., Rosen, S.D., 2019. Cardiovascular effects of psychotic illnesses and antipsychotic therapy. Heart 105, 1852–1859. https://doi.org/10.1136/heartjnl-2017-312107.

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., Leucht, S., 2019. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 394, 939–951. https://doi.org/10.1016/S0140-6736(19)31135-3.

Huppert, J.D., Weiss, K.A., Lim, R., Pratt, S., Smith, T.E., 2001. Quality of life in schizophrenia: contributions of anxiety and depression. Schizophr. Res. 51, 171–180.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Khan, A.Y., Carrithers, J., Preskorn, S.H., Lear, R., Wisniewski, S.R., Rush, A.J., Stegman, D., Kelley, C., Kreiner, K., Nierenberg, A.A., Fava, M., 2006. Clinical and demographic factors associated with DSM-IV melancholic depression. Ann. Clin. Psychiatr. 18, 91–98. https://doi.org/10.1080/10401230600614496.

Khandaker, G.M., Dantzer, R., Jones, P.B., 2017. Immunopsychiatry: important facts. Psychol. Med. 47, 2229–2237. https://doi.org/10.1017/S0033291717000745.

Korver, N., Quee, J.P., Boos, B.M.H., Simons, J.P.C., de Haan, L., GROUP Investigators, 2012. Genetic risk and outcome of psychosis (GROUP), a multi site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. Int. J. Methods Psychiatr. Res. 21, 205–221. https://doi.org/10.1002/mpr.

Kroken, R.A., Sommer, I.E., Steen, V.M., Dieset, I., Johnsen, E., 2019. Constructing the immune signature of schizophrenia for clinical use and research; an integrative review translating descriptives into diagnostics. Front. Psychiatr. 10, 1–16. https://doi.org/10.3389/fpsyt.2018.00753.

Krynicki, C.R., Upthegrove, R., Deakin, J.F.W., Barnes, T.R.E., 2018. The relationship between negative symptoms and depression in schizophrenia: a systematic review. Acta Psychiatr. Scand. 137, 380–390. https://doi.org/10.1111/acps.12873.

Kucerova, J., Babinska, Z., Horska, K., Kotolova, H., 2015. The common pathophysiology underlying the metabolic syndrome, schizophrenia and depression. A review. Biomed. Pap. Med. Fac. Univ. Palacký, Olomouc, Czechoslov 159, 208–214. https://doi.org/10.5507/bp.2014.060.

Lako, I.M., Wigman, J.T., Klaassen, R.M., Slooff, C.J., Taxis, K., Bartels-Velthuis, A.A., Bruggeman, R., Wiersma, D., Cahn, W., Kahn, R.S., de Haan, L., Meijer, C.J., Myin-Germeys, I., van Os, J., 2014. Psychometric properties of the self-report version of the Quick inventory of depressive symptoms (QIDS-SR16) questionnaire in patients with schizophrenia. BMC Psychiatr. 14 (247) https://doi.org/10.1186/s12888-014-0247-2.

Lamers, F., Milaneschi, Y., de Jonge, P., Giltay, E.J., Penninx, B.W.J.H., 2018. Metabolic and inflammatory markers: associations with individual depressive symptoms. Psychol. Med. 48, 1102–1110. https://doi.org/10.1017/S0033291717002483.

Lançon, C., Auquier, P., Reine, G., Bernard, D., Addington, D., 2001. Relationships between depression and psychotic symptoms of schizophrenia during an acute episode and stable period. Schizophr. Res. 47, 135–140. https://doi.org/10.1016/S0920-9964(00)00002-5.

Lee, E.E., Hong, S., Martin, A.S., Eyler, L.T., Jeste, D.V., 2017. Inflammation in schizophrenia: cytokine levels and their relationships to demographic and clinical variables. Am. J. Geriatr. Psychiatr. 25, 50–61. https://doi.org/10.1016/j.jagp.2016.09.009.

Majadas, S., Olivares, J., Galan, J., Diez, T., 2012. Prevalence of depression and its relationship with other clinical characteristics in a sample of patients with stable schizophrenia. Compr. Psychiatr. 53, 145–151. https://doi.org/10.1016/j.comppsych.2011.03.009.

Maurer, K., Trendler, G., Schmidt, M., an der Heiden, W., Könnecke, R., Häfner, H., 2006. Schizophrenie und Depression. Nervenarzt 77, 809–822. https://doi.org/10.1007/s00115-005-1920-y.

Mitchell, A.J., Vancampfort, D., Sweers, K., Van Winkel, R., Yu, W., De Hert, M., 2013. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders-a systematic review and meta-analysis. Schizophr. Bull. 39, 306–318. https://doi.org/10.1093/schbul/sbr148.

Müller, M.J., Szegedi, A., Wetzel, H., Benkert, O., 2001. Depressive factors and their relationships with other symptom domains in schizophrenia, schizoaffective disorder, and psychotic depression. Schizophr. Bull. 27, 19–28.

Penninx, B.W.J.H., 2017. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. Neurosci. Biobehav. Rev. 74, 277–286. https://doi.org/10.1016/j.neubiorev.2016.07.003.

Penninx, B.W.J.H., Beekman, A.T.F., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., De Jong, P.J., Van Marwijk, H.W.J., Assendelft, W.J.J., van der Meer, K., Verhaak, P., Wensing, M., de Graaf, R., Hoogendijk, W.J., Ormel, J., van Dyck, R., 2008. The Netherlands study of depression and anxiety (NESDA): rationale, objectives and methods. Int. J. Methods Psychiatr. Res. 17, 121–140. https://doi.org/10.1002/mpr.256.

Penninx, B.W.J.H., Lange, S.M.M., 2018. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. Dialogues Clin. Neurosci. 20, 63–73. https://doi.org/10.1038/jid.2015.269.

Penninx, B.W.J.H., Milaneschi, Y., Lamers, F., Vogelzangs, N., 2013. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med 11 (129). https://doi.org/10.1186/1741-7015-11-129.

Rabany, L., Weiser, M., Werbeloff, N., Levkovitz, Y., 2011. Assessment of negative symptoms and depression in schizophrenia: revision of the SANS and how it relates to the PANSS and CDSS. Schizophr. Res. 126, 226–230. https://doi.org/10.1016/j.schres.2010.09.023.

Rahim, T., Rashid, R., 2017. Comparison of depression symptoms between primary depression and secondary-to-schizophrenia depression. Int. J. Psychiatr. Clin. Pract. 21, 314–317. https://doi.org/10.1080/13651501.2017.1324036.

Roest, A.M., Thombs, B.D., Grace, S.L., Stewart, D.E., Abbey, S.E., de Jonge, P., 2011. Somatic/affective symptoms, but not cognitive/affective symptoms, of depression after acute coronary syndrome are associated with 12-month all-cause mortality. J. Affect. Disord. 131, 158–163. https://doi.org/10.1016/j.jad.2010.11.018.

Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M.E., Kocsis, J.H., Keller, M.B., 2003. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol. Psychiatr. 54, 573–583. https://doi.org/10.1016/S0006-3223(03)01866-8.

Schaakxs, R., Comijs, H.C., Lamers, F., Beekman, A.T.F., Penninx, B.W.J.H., 2017. Age-related variability in the presentation of symptoms of major depressive disorder. Psychol. Med. 47, 543–552. https://doi.org/10.1017/S0033291716002579.

Schennach, R., Obermeier, M., Seemüller, F., Jäger, M., Schmauss, M., Laux, G., Pfeiffer, H., Naber, D., Schmidt, L.G., Gaebel, W., Klosterkötter, J., Heuser, I., Maier, W., Lemke, M.R., Rüther, E., Klingberg, S., Gastpar, M., Riedel, M., Möller, H. J., 2012. Evaluating depressive symptoms in schizophrenia: a psychometric comparison of the calgary depression scale for schizophrenia and the Hamilton depression rating scale. Psychopathology 45, 276–285. https://doi.org/10.1159/000336729.

Schennach, R., Riedel, M., Obermeier, M., Seemüller, F., Jäger, M., Schmauss, M., Laux, G., Pfeiffer, H., Naber, D., Schmidt, L.G., Gaebel, W., Klosterkötter, J., Heuser, I., Maier, W., Lemke, M.R., Rüther, E., Klingberg, S., Gastpar, M., Möller, H. J., 2015. What are depressive symptoms in acutely ill patients with schizophrenia spectrum disorder? Eur. Psychiatr. 30, 43–50. https://doi.org/10.1016/j.eurpsy.2014.11.001.

Simonsen, C., Sundet, K., Vaskinn, A., Ueland, T., Romm, K.L., Hellvin, T., Melle, I., Friis, S., Andreassen, O.A., 2010. Psychosocial function in schizophrenia and bipolar disorder: relationship to neurocognition and clinical symptoms. J. Int. Neuropsychol. Soc. 16, 771–783. https://doi.org/10.1017/S1355617710000573.

Siris, S.G., Bench, C., 2003. Depression and schizophrenia. In: Hirsch, S.R., Weinberger, D.R. (Eds.), Schizophrenia. Blackwell Science Ltd, Oxford, UK, pp. 142–167. https://doi.org/10.1002/9780470987353.ch9.

Sönmez, N., Røssberg, J.I., Evensen, J., Barder, H.E., Haahr, U., ten Velden Hegelstad, W., Joa, I., Johannessen, J.O., Langeveld, H., Larsen, T.K., Melle, I., Opjordsmoen, S., Rund, B.R., Simonsen, E., Vaglum, P., Mcglashan, T., Friis, S., 2016. Depressive symptoms in first-episode psychosis: a 10-year follow-up study. Early Interv. Psychiatry 10, 227–233. https://doi.org/10.1111/eip.12163.

Upthegrove, R., Marwaha, S., Birchwood, M., 2017. Depression and schizophrenia: cause, consequence, or trans-diagnostic issue? Schizophr. Bull. 43, 240–244. https://doi.org/10.1093/schbul/sbw097.

Van Eck, R.M., Burger, T.J., Vellinga, A., Schirmbeck, F., De Haan, L., 2018. The relationship between clinical and personal recovery in patients with schizophrenia spectrum disorders: a systematic review and meta-analysis. Schizophr. Bull. 44, 631–642. https://doi.org/10.1093/schbul/sbx088.

van Rooijen, G., Isvoranu, A.M., Kruijt, O.H., van Borkulo, C.D., Meijer, C.J., Wigman, J. T.W., Ruhé, H.G., de Haan, L., Bruggeman, R., Cahn, W., de Haan, L., Kahn, R.S., Meijer, C., Myin-Germeys, I., van Os, J., Bartels-Velthuis, A.A., 2018. A state-independent network of depressive, negative and positive symptoms in male patients with schizophrenia spectrum disorders. Schizophr. Res. 193, 232–239. https://doi.org/10.1016/j.schres.2017.07.035.

Wardenaar, K.J., Van Veen, T., Giltay, E.J., Den Hollander-Gijsman, M., Penninx, B.W.J. H., Zitman, F.G., 2010. The structure and dimensionality of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in patients with depressive disorders and healthy controls. J. Affect. Disord. 125, 146–154. https://doi.org/10.1016/j.jad.2009.12.020.

Wing, J.K., Babor, T., Brugha, T., Burke, J., Cooper, J.E., Giel, R., Jablenski, A., Regier, D., Sartorius, N., 1990. SCAN Schedules for clinical assessment in Neuropsychiatry. Arch. Gen. Psychiatr. 47 (589) https://doi.org/10.1001/archpsyc.1990.01810180089012.

World Health Organisation, 1990. Composite international diagnostic interview. Geneva world heal. Organ.