The association between sleep disturbances and negative symptom severity in patients with non-affective psychotic disorders, unaffected siblings and healthy controls

Sophia A.M. de Crom a, Lieuwe de Haan a,b,1, Frederike Schirmbeck a,b,1,* , GROUP investigators 2

a Department of Psychiatry, Amsterdam University Medical Centre, University of Amsterdam, Meibergdreef 5, 1105 AZ Amsterdam, the Netherlands
b Arkin Institute for Mental Health, Klaprozenweg 111, 1033 NN Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Depressive symptoms
Negative symptoms
Psychotic disorders
Relatives
Sleep disorders

ABSTRACT

Sleep disturbances in patients with psychotic disorders are common and associated with poor clinical outcomes, but research on negative symptoms is limited. This study aimed to examine the association between subjective sleep disturbances and negative symptoms in 525 patients with non-affective psychotic disorders, 569 unaffected siblings and 265 healthy controls (HC) from the Genetic Risk and Outcome of Psychosis (GROUP) study. Several aspects of subjective sleep disturbances were assessed: sleep satisfaction, sleep onset insomnia, midnocturnal insomnia, early morning insomnia, and hypersomnia. Regression analyses revealed significant negative associations between sleep satisfaction and negative symptoms in all three groups. In addition, significant associations with sleep onset insomnia and hypersomnia were found in patients and with early morning insomnia and hypersomnia in siblings. Exploratory mediation analyses showed that depressive symptoms partly mediated all associations on the subclinical level in siblings and healthy controls, whereas only the association with sleep onset insomnia was mediated in patients. The results of this study implicate specific sleep disturbances and depressive symptoms as potential targets in prevention or intervention strategies focused on negative symptoms in individuals suffering from, or at risk of non-affective psychotic disorders.

1. Introduction

There is a growing interest in and recognition of the role of sleep disturbances in the pathophysiology of psychotic disorders. Sleep disturbances are common in psychotic disorders with 30–80% of patients reporting them (Cohrs, 2008; Goines et al., 2019). The most commonly reported subjective sleep disturbances include difficulties falling asleep (sleep onset insomnia or increased latency), difficulties with sleep maintenance, a reduction in total sleep time, multiple awakenings during sleep (midnocturnal insomnia or nocturnal awakenings), and early morning insomnia (early morning awakenings)(Cohrs, 2008; Zanini et al., 2013).

The mechanisms by which sleep interacts with other clinical correlates remain unclear, although evidence suggests that patients with a psychotic disorder and sleep disturbances experience more severe symptoms than patients without sleep disturbances (Afonso et al., 2014; Poe et al., 2017). Impaired sleep in patients has been associated with important clinical outcomes including poorer coping (Ritsner et al., 2004), higher distress and reduced quality of life (Fond et al., 2020; Hofstetter et al., 2005), increased frequency of depression (Palmese et al., 2011) and completed suicide (Pompili et al., 2009). Other observed effects are reduced social functioning and poorer cognitive performance (Forest et al., 2007; Mulligan et al., 2016). Sleep disturbances are suggested to occur irrespective of medication status (Chouinard et al., 2004; Monti and Monti, 2005; Poulin et al., 2003) or phase of the clinical course (Monti and Monti, 2005). Accordingly, sleep disturbances have been found to precede relapse in chronic patients (Monti and Monti, 2005), and have been revealed as an important factor predicting transitioning from an ultra-high risk state to a first psychotic episode (Davies et al., 2017; Goines et al., 2019; Kasanova et al., 2019; Ruhrmann et al., 2016; Stowkowy et al., 2013; Tan and Ang, 2001; Zanini et al., 2013). Even in first-degree relatives of patients, sleep is...
observed to be disturbed compared to healthy controls (HC) (Manoach et al., 2014; Sarkar et al., 2010; Schilling et al., 2017).

Emphasising the clinical importance, sleep disturbances in psychotic disorders are perceived as highly disturbing, with negative impact on well-being, and they are often reported as the primary motivation to seek treatment (Auslander and Jeste, 2002; Waite et al., 2016). The association between sleep disturbances (including sleep quality (Kasanova et al., 2019; Mulligan et al., 2016)) and positive symptoms has been extensively demonstrated (Freeman et al., 2012; Poulin et al., 2003, 2008; Reeve et al., 2015; Sarkar et al., 2010; Tandon et al., 1992; Yang and Winkelman, 2006), on the clinical as well as subclinical level (Goines et al., 2019; Lunsford-Avery et al., 2017b, 2015; Poe et al., 2017; Reeve et al., 2018a), and across several stages of the psychotic disorder (Kasanova et al., 2019; Reeve et al., 2018b). However, although (persistent) negative symptoms contribute to a poorer prognosis (Millec et al., 2005; Tandon et al., 2005), their association with sleep disturbances has been less investigated and methodological shortcomings are often limiting the validity of conclusions (Monti and Monti, 2005).

Studies with objective measurements found associations between negative symptoms and slow wave sleep deficit (Ganguli et al., 1987; Keshavan et al., 1995; Tandon et al., 1989; van Kammen et al., 1988), rapid eye movement latency (Keshavan et al., 1995; Tandon et al., 2000, 1989, 1992), halve-wave counts of higher-amplitude delta waves (Kajimura et al., 1996; Monti and Monti, 2004), alpha activity (Poulin et al., 2008) and stage 1 sleep percentage (Yang and Winkelman, 2006) in patients with psychotic disorders. Regarding subjective sleep measures, a recent study of Blanchard et al. (Blanchard et al., 2020) reported subjectively more severe sleep disturbances related to higher negative symptom severity, and a study of Yamashita et al. (Yamashita et al., 2004) has shown significant improvement of negative symptoms associated with the improvement of subjective sleep quality after changing from conventional to atypical antipsychotic medication. This last study did not include a control group. Accordingly, a limited number of studies reported on the association between sleep disturbances and subclinical negative symptoms in individuals at ultra-high risk of psychosis (UHR) (Lunsford-Avery et al., 2017a, 2017b, 2013; Poe et al., 2017). In the study of Poe et al., (Poe et al., 2017) difficulties falling asleep, early awakening, sleep pattern disruptions and sleeping more than considered average (hypersomnia) were significantly associated with negative symptoms in UHR individuals. In different studies of Lunsford-Avery et al., circadian disturbances (Lunsford-Avery et al., 2017b), increased latency, decreased sleep duration and decreased sleep quality (Lunsford-Avery et al., 2013) were found to be related with higher negative symptom severity. All these studies had small sample sizes, and studies investigating associations between subjective sleep disturbances and negative symptoms in patients with psychotic disorders did not differentiate between specific types of sleep disturbances. Investigating specific domains of subjective sleep disturbances might however provide valuable information for potential targets for prevention or intervention strategies in psychotic disorders (Lunsford-Avery et al., 2013).

Furthermore, although some studies investigated the association in individuals at ultra-high risk of psychosis (UHR) (Lunsford-Avery et al., 2017a, 2013; Poe et al., 2017), to our knowledge, no study has investigated the association between self-reported sleep disturbances and symptom severity in first-degree relatives of patients with a psychotic disorder. The inclusion of such a sample would generate, however, a multi-site longitudinal naturalistic cohort study focussing on gene – environment interaction with assessments at baseline and follow-up after three and six years. The current study has a cross-sectional design, using data from the 3-year follow-up assessment, when sleep measurements were performed. Patients, siblings and HC with complete data on outcome measures regarding sleep disturbances and negative symptoms were included. The procedures of recruitment and population characteristics are described in detail elsewhere (Korver et al., 2012). In short, inclusion criteria were (1) age range of 16–50 years and (2) good command of the Dutch language. Patients had to meet DSM-IV-TR criteria for a non-affective psychotic disorder (APA, 2000), and in siblings and HC, the absence of a lifetime psychotic disorder was mandatory. Patients were recruited by clinicians from four university study sites and their surrounding mental health care facilities in the Netherlands and Belgium. HC were selected through a system of random mailings to addresses in the catchment areas of the cases. Assessments consisted of a large test battery of clinical interviews, cognitive tests and questionnaires, and were administered at the participating health care facility by trained investigators.

After receiving verbal and written information about the study, all participants provided informed consent prior to their inclusion. The study was approved by the accredited Medical Ethics Review Committee (METC).

2.2. Measurements

2.2.1. Clinical symptoms

Sociodemographic data as well as medication use during the last 3 years was evaluated using a self-reported questionnaire, specifically developed for the GROUP-study. Negative and depressive symptom severity in patients, siblings and HC was assessed with the Community Assessment of Psychotic Experiences (CAPE). The CAPE is a self-reported questionnaire for the measurement of psychotic experiences with subscales for positive, negative, and depressive symptoms (Konings et al., 2006; Mark and Touboulou, 2016). Items are rated in terms of frequency on a 4-point Likert scale from 0 (never) to 3 (almost always). A mean total score was calculated for the subscales if at least 14/20, 9/14, and 5/8 items were available for the positive, negative, and depressive symptoms respectively. To compare the self-reported outcomes in patients with a clinician-rated instrument, the five factor model (van der Gaag et al., 2006a, 2006b) of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), was used in addition. The dimensions of positive and negative symptoms and emotional distress of this model were used to measure the severity of positive, negative, and depressive symptoms.
significantly contributed to the model while controlling for variables in were first added to the model in steps, investigating whether they were most severe in patients. Pairwise comparisons revealed that pa

symptoms.

2.2.2. Sleep disturbances

Data on sleep disturbances were extracted from the Quick Inventory of Depressive Symptoms (QIDS-SR) (Rush et al., 2003), and the World Health Organisation Quality of Life-BREF (WHOQOL-BREF) (Trompenaars et al., 2005), both self-reported questionnaires. Sleep disturbances on the QIDS-SR are subdivided in 4 specific disturbances: sleep onset insomnia (QIDS 1), midnocturnal insomnia (QIDS 2), early morning insomnia (QIDS 3), and hypersomnia (QIDS 4). Items are rated on a 4-point Likert scale from 0 (absent) to 3 (severe). Good internal consistency of the QIDS has been demonstrated in patients with a psychotic disorder (Lako et al., 2014). The item on the WHOQOL-BREF concerns the question ‘How satisfied are you with your sleep?’ and is rated on a 5-point Likert scale from 1 (very dissatisfied) to 5 (very satisfied). The WHOQOL-BREF is observed to be an adequate measurement assessing quality of life with high construct validity and reliability in a Dutch psychiatric outpatient population (Trompenaars et al., 2005). The different items of the WHO and QIDS questionnaire with their rating scales are presented in Table S1.

2.2.3. Covariates

To account for possible confounding effects, covariates were selected a priori. Age and gender, cannabis use (Goines et al., 2019), positive symptoms (Funar-Poli et al., 2015; Krause et al., 2018; Peralta et al., 2000; Reeve et al., 2015; Stauffer et al., 2012), and antipsychotic medication (AP) use (Cohrs, 2008; Krause et al., 2018; Monti and Monti, 2004) were added as covariates because of the presumed association of these variables with sleep disturbances and negative symptoms. Cannabis use was defined as a positive response on cannabis use in the last 12 months as assessed with the Composite International Diagnostic Interview (CIDI) (WHO, 1990). In patients, the main AP was categorised according to the ‘Drowsiness’ and ‘Hypersleep’ criteria of the Personal Antipsychotic Choice (PAC)-index (van Dijk et al., 2018). In this tool, adverse effects of AP are categorised based on available evidence. A higher rank is representing a larger effect. No or unknown AP use was categorised with a zero.

2.3. Statistical analyses

In order to evaluate differences between patients, siblings and HC regarding sociodemographic and clinical characteristics, one-way ANOVA analyses and chi-square tests were conducted.

Normal probability plots and scatterplots of standardised residuals were used to check the assumptions of normality, linearity and homoscedasticity. The assumption of multicollinearity was checked using Pearson Correlation and Collinearity Statistics (Tolerance and Variance inflation factor). Outliers, defined as cases exceeding more than three box-lengths from the edge of the box of the boxplot (in SPSS indicated with an asterisk), were removed: 15 patients, 23 siblings and 13 HC.

In case of violation of the assumption of normal distribution, Kruskal-Wallis tests were performed (which turned out to be the case for all sleep variables). In case of violation of the assumption of homogeneity of variance, the F-value was corrected using the Welch’s test. Then, the Games-Howell’s test instead of the Bonferroni’s test was used for pairwise comparisons to adjust for multiple comparisons, minimising the risk of type I errors (turning out to be the case for positive symptoms). Because of the large sample sizes, homogeneity of variance was assumed if the ratio of the largest and smallest variance of groups did have a maximum of 4 (de Vocht, 2019). Cross-sectional associations between sleep disturbances and negative symptoms were assessed using hierarchical linear multiple regression, with sleep disturbances as predictors and negative symptom severity (on the CAPE and PANSS, see section 2.2.1) as outcome variable. Covariates were first added to the model in steps, investigating whether they significantly contributed to the model while controlling for variables in previous steps. As a final step, sleep disturbances were added to the model.

To examine the possible mediating effect of depressive symptoms on the association between sleep disturbances and negative symptom severity, maximum likelihood regression mediation analyses were performed using PROCESS version 3.4.1 (Preacher and Hayes, 2008). PROCESS is a tool for moderation and mediation analyses using path-based analyses, and generates effect coefficients and confidence interval estimates based on bootstrapping (Preacher and Hayes, 2008). In the current study, sleep disturbances were used as predictors, negative symptoms as outcome, and depressive symptoms as a potential mediator. The paths are shown in Figure S1. The standardised indirect effect (‘the index of mediation’) is presented because this coefficient can be compared across different mediation models (Field, 2014b). Mediation was concluded if the strength of the association between the predictor and the outcome was reduced by including the mediator in the model (the direct effect was smaller than the total effect), and the range of the confidence interval of the indirect effect (and thus of the index of mediation) did not include zero (Field, 2014b). The pathways were bootstrapped using the mean of 5000 estimates and a 95% confidence interval was maintained. To account for confounding effects and to explore the mediating effects of depressive symptoms on the association between one specific sleep disturbance and negative symptoms, significant covariates from the final regression analyses, including the other significant sleep disturbances, were added to the models.

Unless stated otherwise, a two-tailed significance level of $p \leq 0.05$ was applied. All analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics 26). GROUP data release 7.0 was used for data analyses.

3. Results

3.1. Sample characteristics and group differences

Comparisons regarding sociodemographic characteristics and outcome variables between patients ($N=525$), siblings ($N=569$) and HC ($N=265$) are presented in Table 1.

Pairwise comparisons showed a higher proportion of male gender and a higher percentage of cannabis use in patients compared to siblings and HC. Patients scored lower on IQ, years of education, social functioning, and quality of life. Patients scored higher on positive, negative, and depressive symptoms of the CAPE compared to siblings and HC. Siblings and HC only significantly differed in IQ, years of education, and social functioning with siblings showing lower scores.

Regarding sleep, all analysed sleep disturbances, except for midnocturnal insomnia (QIDS 2), showed significant group differences and were most severe in patients. Pairwise comparisons revealed that patients reported significantly lower sleep satisfaction and more severe sleep onset insomnia (QIDS 1), early morning insomnia (QIDS 3), and hypersomnia (QIDS 4) compared to siblings and HC. Siblings and HC only significantly differed in IQ, years of education, and social functioning with siblings showing lower scores.

Regarding sleep, all analysed sleep disturbances, except for midnocturnal insomnia (QIDS 2), showed significant group differences and were most severe in patients. Pairwise comparisons revealed that patients reported significantly lower sleep satisfaction and more severe sleep onset insomnia (QIDS 1), early morning insomnia (QIDS 3), and hypersomnia (QIDS 4) compared to siblings and HC. Siblings and HC only significantly differed in severity of sleep onset insomnia (QIDS 1) (Continuity Correction $= 7.47$, $p$-value $= 0.006$, phi coefficient $= 0.097$).

3.2. The association between sleep disturbances and negative symptom severity

Hierarchical multiple regression analyses were used to assess the association of different sleep disturbances and negative symptom severity, after controlling for age, gender, cannabis use, positive symptoms, and, in patients, sedating potential of APs. Age and gender were entered as the first step; the other covariates were entered in above-mentioned order. The sleep disturbances were entered at the final step. The results of the final steps are presented in Table 2. The detailed models with all subsequent steps are presented in Table S2, S3, S4 for patients, siblings, and HC respectively.
3.3. Mediation of depressive symptoms

Separate mediation analyses were performed for patients, siblings and HC to examine the possible mediating effect of depressive symptoms on significant associations between sleep disturbances and negative symptom severity. Significant covariates from the regression analyses were added to the models (see Table 2, Table S5). The mediation analyses are presented in Table 3.

In patients, depressive symptoms partially mediated the association between sleep onset insomnia (QIDS 1) and negative symptoms, but not the associations with sleep satisfaction and hypersomnia (QIDS 4). In siblings and HC, analyses revealed partially mediating effects of depressive symptoms for all associations. Direct effects remained significant, except for the association between early morning insomnia (QIDS 1) and negative symptoms, but not between sleep onset insomnia (QIDS 1) and negative symptoms. Significant covariates from the regression analyses were added to the models (see Table 2, Table S5). The mediation analyses are presented in Table 3.

In patients, depressive symptoms partially mediated the association between sleep onset insomnia (QIDS 1) and negative symptoms, but not the associations with sleep satisfaction and hypersomnia (QIDS 4). In siblings and HC, analyses revealed partially mediating effects of depressive symptoms for all associations. Direct effects remained significant, except for the association between early morning insomnia (QIDS 3) and negative symptoms in siblings. The indexes of mediation of the mediation analyses for patients, siblings and HC were comparable.

In patients, repeating the analyses with the PANSS negative subscale as outcome variable (Table S6), analyses revealed a partially mediating effect of depressive symptoms for the association between hypersomnia (QIDS 4) and negative symptoms. Direct effects remained significant, except for the association with sleep onset insomnia (QIDS 1). The indexes of mediation were smaller compared to the mediation analyses with the CAPE as outcome variable.

4. Discussion

To the best of our knowledge, the current study is the first to investigate the association between specific, self-reported sleep disturbances and negative symptom severity in patients with non-affective psychotic disorders, siblings and HC. Data was obtained from a large cohort study representing the prevalence of help-seeking patients with a
Table 2
Final steps of the hierarchal multiple regression models of predictors of negative symptoms in patients, siblings and healthy controls. 95% confidence intervals are reported in parentheses.

|                | B     | SE B  | Beta  | P-value |
|----------------|-------|-------|-------|---------|
| Patients (N = 506) |       |       |       |         |
| Constant        | 0.747 | 0.141 | 0.000 |         |
| Age             | 0.001 | 0.003 | 0.012 | 0.746   |
| Gender          | 0.096 | 0.051 | 0.070 | 0.062   |
| Cannabis use    | 0.097 | 0.048 | 0.076 | 0.045   |
| CAPE Positive symptoms | 0.465 | 0.046 | 0.402 | 0.000   |
| AP use          | 0.037 | 0.020 | 0.072 | 0.057   |
| WHO sleep satisfaction | −0.061 | 0.021 | −0.121 | 0.004  |
| QIDS 1 – Sleep onset insomnia | 0.068 | 0.020 | 0.138 | 0.001   |
| QIDS 2 – Midnocturnal insomnia | 0.044 | 0.023 | 0.079 | 0.052   |
| QIDS 3 – Early morning insomnia | −0.038 | 0.027 | −0.058 | 0.166   |
| QIDS 4 – Hypersomnia | 0.093 | 0.023 | 0.157 | 0.000   |
| Siblings (N = 541) |       |       |       |         |
| Constant        | 0.434 | 0.099 | 0.000 |         |
| Age             | 0.004 | 0.002 | 0.093 | 0.016   |
| Gender          | 0.000 | 0.002 | 0.000 | 0.990   |
| Cannabis use    | 0.006 | 0.041 | 0.061 | 0.110   |
| CAPE Positive symptoms | 1.278 | 0.127 | 0.378 | 0.000   |
| WHO sleep satisfaction | −0.083 | 0.018 | −0.198 | 0.000   |
| QIDS 1 – Sleep onset insomnia | 0.014 | 0.018 | 0.032 | 0.431   |
| QIDS 2 – Midnocturnal insomnia | −0.008 | 0.017 | 0.018 | 0.642   |
| QIDS 3 – Early morning insomnia | 0.086 | 0.036 | 0.092 | 0.017   |
| QIDS 4 – Hypersomnia | 0.147 | 0.027 | 0.204 | 0.000   |
| Healthy Controls (N = 247) |       |       |       |         |
| Constant        | 0.375 | 0.114 | 0.001 |         |
| Age             | 0.005 | 0.002 | 0.172 | 0.002   |
| Gender          | 0.007 | 0.034 | 0.012 | 0.828   |
| Cannabis use    | 0.031 | 0.047 | 0.036 | 0.509   |
| CAPE Positive symptoms | 1.493 | 0.166 | 0.496 | 0.000   |

Abbreviations: AP = antipsychotic medication; CAPE = Community Assessment of Psychic Experiences; N = Number; QIDS = Quick Inventory of Depressive Symptoms; SE = Standard Error; WHO = World Health Organisation.

Table 2 (continued)

|                      | B     | SE B  | Beta  | P-value |
|----------------------|-------|-------|-------|---------|
| WHO sleep satisfaction | −0.076 | 0.021 | −0.209 | 0.000   |
| QIDS 1 – Sleep onset insomnia | 0.049 | 0.028 | 0.103 | 0.079   |
| QIDS 2 – Midnocturnal insomnia | −0.003 | 0.019 | −0.009 | 0.867   |
| QIDS 3 – Early morning insomnia | 0.020 | 0.084 | 0.013 | 0.808   |
| QIDS 4 – Hypersomnia | −0.036 | 0.029 | −0.066 | 0.216   |

non-affective psychotic disorder (Korver et al., 2012). By including unaffected and unmedicated siblings, we were able to investigate associations in participants with an increased disorder liability with fewer illness related confounding effects.

Patients reported more severe sleep disturbances compared to siblings and HC. Regarding hypothesised associations between sleep disturbances and negative symptom severity on a clinical and subclinical level, lower subjective sleep satisfaction was associated with higher negative symptom severity in all three groups. Furthermore, significant associations with sleep onset insomnia (QIDS 1) and hypersomnia (QIDS 4) were found in patients and with early morning insomnia (QIDS 3) and hypersomnia (QIDS 4) in siblings. Comparable associations in patients were revealed when negative symptoms were assessed with the clinician-rated PANSS. Finally, exploratory mediation analyses revealed the following results: in patients, the association between sleep onset insomnia (QIDS 1) and negative symptoms was partially mediated by depressive symptoms. No mediating effect was found on the associations with sleep satisfaction and hypersomnia (QIDS 4). On the subclinical level, all associations were mediated by depressive symptoms. On both the clinical and subclinical level, remaining direct associations between sleep satisfaction and hypersomnia (QIDS 4) and negative symptoms were revealed.

Differences in the severity of subjective sleep disturbances between patients, first-degree relatives and HC have been described before in a study of Sarkar et al. (Sarkar et al., 2010). In line with our results, in that study, sleep was more disturbed in patients. Regarding current results concerning the association between more severe subjective sleep disturbances and higher negative symptom severity; associations were also previously demonstrated in UHR individuals (Lunsford-Avery et al., 2017a; Poe et al., 2017), even after controlling for depressive symptoms (Lunsford-Avery et al., 2013), and on the clinical level in the study of Blanchard et al. (Blanchard et al., 2020). The current study extends the findings of the latter study in several ways. We controlled for relevant a priori selected confounders, other sleep disturbances, and the mediating effect of depressive symptoms. Moreover, we investigated specific associations by subdividing the self-reported sleep disturbances offering a more detailed understanding of the associations and possibly contributing to the unravelling of risk factors (or effects) of negative symptoms. For example, we found that direct effects of sleep satisfaction and hypersomnia (QIDS 4) remained significant independent of depressive symptoms. No mediating effect was found on the associations by subdividing the self-reported sleep disturbances offering a more detailed understanding of the associations and possibly contributing to the unravelling of risk factors (or effects) of negative symptoms. The strong association between hypersomnia (QIDS 4) and negative symptoms could however be due to overlap in measured concepts in terms of lack of energy or interest, related to social withdrawal and (indirectly) to staying in bed and excessive sleepiness. The association with sleep satisfaction could be explained by highly prioritising sleep: sleep improvement in patients is often stated amongst the highest
whether observed negative symptoms are primary or secondary (Car et al., 2018; Peralta et al., 2000), and, in the case of medication use, were revealed in siblings and HC, supporting the independence from negative symptom severity (Watson et al., 2018).

The mediators between depressive and negative symptoms has consistently been reported including the sedative capacity of APs as a covariate to the statistical model. The effect of APs could not be entirely explained by sleep disturbances. These results suggest that targeting specific sleep disturbances in prevention or intervention strategies might contribute to the reduction of negative symptoms in psychotic disorders. Furthermore, depressive symptoms seem to play a role in the association between sleep disturbances and negative symptom severity. Hence, in addition to research concerning the impact of improving sleep perceptions, research on the impact of depressive symptoms appears to be of importance (Scott et al., 2017).

Table 3

| X               | X to M – a path | P-value | M to Y – b path | P-value | Total effect – c path | P-value | Direct effect –c’ path | P-value | Index of mediation (95% CI) |
|-----------------|-----------------|---------|-----------------|---------|-----------------------|---------|------------------------|---------|---------------------------|
| Patients        | WHO sleep satisfaction | -0.0372 | 0.0712 | 0.6024 | <0.001 | -0.0563 | 0.0066 | -0.0339 | 0.0413 | -0.0447 (−0.0962, 0.0074) |
| (N = 506)       | QIDS 1 – Sleep onset insomnia | 0.0899 | <0.001 | 0.6024 | <0.001 | 0.0675 | 0.0009 | 0.0134 | 0.4194 | 0.1062 (0.0564, 0.1630) |
|                 | QIDS 4 – Hypersomnia | 0.0170 | 0.4511 | 0.6024 | <0.001 | 0.0909 | 0.0001 | 0.0807 | <0.001 | 0.0172 (−0.0286, 0.0619) |
| Siblings        | WHO sleep satisfaction | -0.0679 | <0.001 | 0.7152 | <0.001 | -0.0889 | <0.001 | -0.0404 | 0.0007 | -0.1168 (−0.1708, −0.0625) |
| (N = 546)       | QIDS 3 – Early morning insomnia | 0.1168 | 0.0005 | 0.7152 | <0.001 | 0.0902 | 0.0111 | 0.0067 | 0.8007 | 0.0891 (0.0283, 0.1500) |
|                 | QIDS 4 – Hypersomnia | 0.1235 | <0.001 | 0.7152 | <0.001 | 0.1524 | <0.001 | 0.0641 | 0.0015 | 0.1223 (0.0678, 0.1778) |
| Healthy Controls| WHO sleep satisfaction | -0.0832 | 0.0001 | 0.6245 | <0.001 | -0.0873 | <0.001 | -0.0354 | 0.0133 | -0.1424 (−0.2194, -0.0636) |
| (N = 252)       | Abbreviations: CI = Confidence Interval; N = Number; QIDS = Quick Inventory of Depressive Symptoms; WHO = World Health Organisation. |

Priorities during treatment (Auslander and Jeste, 2002) and sleep considerably contributes to life satisfaction (Ritsner et al., 2004). As a next step, lower quality of life has been associated with increased negative symptom severity (Watson et al., 2018).

Furthermore, extending previous literature, comparable associations were revealed in siblings and HC, supporting the independence from disease status or treatment factors on the association between sleep disturbances and the severity of negative symptoms. Additionally, a remarkable finding was the only trend significant contribution of AP on this association in patients. AP use is a notorious confounder because of the combination of direct and indirect effects on both sleep disturbances (Cohrs, 2008; Monti and Monti, 2004) and negative symptoms (Krause et al., 2018). Regarding negative symptoms, it is hard to disentangle whether APs improve primary or secondary negative symptoms (Krause et al., 2018; Peralta et al., 2000), and, in the case of medication use, whether observed negative symptoms are primary or secondary (Carpenter et al., 1988; Fusar-Poli et al., 2015; Kirkpatrick et al., 2006; Nielsen et al., 2018; Stauffer et al., 2012). In current study, the potential impact of AP on secondary negative symptoms was accounted for by including the sedative capacity of APs as a covariate to the statistical models. However, potential unreliability of the relatively small effect of AP use could originate in the self-reported medication status, in not accounting for multiple AP use, and in the relatively high functional status of the participants. Moreover, the effect of AP could be partly hidden in the strong confounding effect of positive symptoms.

We need to consider several pathways in the interpretation of the mediating effect of depressive symptoms on the association between sleep disturbances and negative symptoms. On the one hand, sleep disturbances might lead to depressive symptoms (Bao et al., 2017; Hertenstein et al., 2019; Li et al., 2016; Staner, 2010; Watling et al., 2017), and depressive symptoms to negative symptoms such as social withdrawal and the lack of energy. Possible mechanisms of action could be that sleep disturbances erode the ability to positively appraise and cope with stressors (Holstetter et al., 2005), reduce well-being (Fond et al., 2020; Ritsner et al., 2004), and negatively affect the development and maintenance of adaptive emotional processes and mood disorders (Hertenstein et al., 2019; Palagini et al., 2019). A close association between depressive and negative symptoms has consistently been reported (Fitzgerald et al., 2002; Muller et al., 2002; Richter et al., 2019; Upthegrove et al., 2017). On the other hand, depressive symptoms may lead to sleep disturbances. Evolutionarily, for example, negative affect arose as a response to danger, with the subsequent heightening of vigilance to prevent sleeping and thus ensuring safety (Watling et al., 2017). Based on the current cross-sectional findings, directions of causality cannot be concluded, but a bidirectional association seems likely. A coherent and integrated understanding of the role of depressive symptoms within psychotic disorders, therefore, remains subject to future research (Fitzgerald et al., 2002; Ronald and Pain, 2016; Upthegrove et al., 2017). Nevertheless, findings from treatment studies indicate clinical relevant associations: Cognitive Behavioural Therapy for insomnia has been shown to reduce psychotic experiences (as well as negative affect) on both the clinical (Freeman et al., 2015; Waite et al., 2016) and subclinical level (Bradley et al., 2018; Freeman et al., 2017), and the pharmacological improvement of subjective sleep quality has been demonstrated to significantly correlate with the improvement of negative symptoms (Yamashita et al., 2004).

Taken together, we found associations between specific subjective sleep disturbances and negative symptom severity on the clinical and subclinical level, even after controlling for relevant confounders, other sleep disturbances, and the mediating effect of depressive symptoms. At least 7% of the variance in self-reported negative symptoms was explained by sleep disturbances. These results suggest that targeting specific sleep disturbances in prevention or intervention strategies might contribute to the reduction of negative symptoms in psychotic disorders. Furthermore, depressive symptoms seem to play a role in the association between sleep disturbances and negative symptom severity. Hence, in addition to research concerning the impact of improving sleep perceptions, research on the impact of depressive symptoms appears to be of importance (Scott et al., 2017).

4.1. Limitations and subsequent future directions

The results and their interpretation ought to be considered with limitations of the current study in mind. To start, the cross-sectional study design prevents elucidation of causal directions between sleep disturbances and negative symptom severity. Reversed causation needs to be considered as negative symptoms might affect sleep. Therefore, future research is necessary to investigate these associations prospectively. Nevertheless, it may be highlighted that evidence from previous prospective findings support the assumption that insomnia might play a causal role in the occurrence of subclinical symptoms (Freeman et al., 2017).

Also regarding the mediation analyses, although hypothesised mediation effects were based on previous findings and theoretical

Abbreviations: CI = Confidence Interval; N = Number; QIDS = Quick Inventory of Depressive Symptoms; WHO = World Health Organisation.
argumentation, we would like to emphasise that conducting mediation analyses on cross-sectional data prevents drawing causal conclusions, as cross-sectional data does not fulfill the presumption of correct temporal variable ordering in the causal chain of mediation (Fairchild and McDaniel, 2017). Noteworthy, as the mediation analyses were exploratory in nature, we did not correct for multiple testing.

Furthermore, sleep disturbances in the current study were assessed with self-reported measurements whereas objective measurement, polysomnography in particular, is considered to be the gold-standard. Polysomnography is, however, impractical for field use or big sample sizes; the technique is expensive and requires laboratory settings that are known to not accurately reflect habitual sleep patterns. (Lockley et al., 1999) Previous research reported subjective and objective sleep variables to converge well on predicting symptomatology in psychosis (Mulligan et al., 2016), and it has been implicated that sleep perception rather than objective measurements is determinant by revealing an as

CRediT authorship contribution statement

Sophia A.M. de Crom: Conceptualization, Formal analysis, Writing - original draft. Lieuwe de Haan: Conceptualization, Supervision, Writing - review & editing. Frederike Schirrmbeck: Conceptualization, Methodology, Supervision, Writing - review & editing.

Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the current study.

Acknowledgement & Funding

We are grateful for the generosity of time and effort by the patients, their families and healthy subjects. Furthermore, we would like to thank all research personnel involved in the GROUP project, in particular: Joyce van Baaren, Erwin Veerman, Ger Driessen, Truda Driesen, Erna van ’t Hag. The infrastructure for the GROUP study is funded through the Geestkracht programme of the Dutch Health Research Council (ZonMw, grant number 10–000–1001), and matching funds from participating pharmaceutical companies (Lundbeck, AstraZeneca, Eli Lilly, Janssen Cilag) and universities and mental health care organisations (Amsterdam: Academic Psychiatric Centre of the Academic Medical Centre and the mental health institutions: GGZ Ingeest, Arkin, Dijk en Duin, GGZ Rivierduinen, Erasmus Medical Centre, GGZ Noord Holland Noord Groningen: University Medical Centre Groningen and the mental health institutions: Lentis, GGZ Friesland, GGZ Drenthe, Dimence, Mediant, GGNet Warnsveld, Yulius Dordrecht and Parnassia psycho-medical centre The Hague. Maastricht: Maastricht University Medical Centre and the mental health institutions: GGzE, GGZ Breburg, GGZ Oost-Brabant, Vincent van Gogh voor Geestelijke Gezondheid, Mondriaan, Virenze riagg, Zuyderland GGZ, MET ggz, Universitair Centrum Sint-Jozef Kortenberg, CAPRI University of Antwerp, PC Ziekeren Sint-Truiden, PZ Sancta Maria Sint-Truiden, GGZ Overpelt, OPZ Rekem. Utrecht: University Medical Centre Utrecht and the mental health institutions Altrecht, GGZ Centraal and Delta).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.113728.

Appendix 1

The GROUP investigators are: Therese van Amelsvoort (Maastricht University Medical Centre, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht, The Netherlands), Agna A. Bartels-Veltkuis (University of Groningen, University Medical Centre Groningen, University Centre for Psychiatry, Rob Giel Research centre, Groningen, The Netherlands), Richard Bruggeman (University of Groningen, University Medical Centre Groningen, University Centre for Psychiatry, Rob Giel Research centre, Groningen, The Netherlands; University of Groningen, Department of Clinical and Developmental Neuropsychology, Groningen, The Netherlands), Wiepke Cahn (University Medical Centre Utrecht, Department of Psychiatry, Brain Centre Rudolf Magnus, Utrecht University, Utrecht, The Netherlands; Altrecht, General Mental Health Care, Utrecht, The Netherlands), Lieuwe de Haan (Amsterdam UMC, University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands; Arkin, Institute for Mental Health, Amsterdam, The Netherlands), Frederike Schirrmbeck (Amsterdam UMC, University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands; Arkin, Institute for Mental Health, Amsterdam, The Netherlands), Claudia J.P. Simons (Maastricht University Medical Centre, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht, The Netherlands; GGzE Institute for Mental Health Care, Eindhoven, The Netherlands), Jim van Os (University Medical Centre Utrecht, Department of Psychiatry, Brain Centre Rudolf Magnus, Utrecht University, Utrecht, The Netherlands; King’s College London, King’s Health Partners, Department of Psychology Studies, Institute of Psychiatry, London, United Kingdom).
