Synopsis for EU-GEI WP5 Publication

Synopsis no.: *S5.19*

Preliminary title:

Prospective associations between self-reported sleep, subtle psychotic experiences and the transition to first-onset psychosis in young people at ultra-high risk (UHR)

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Publication category: 3
Publications from a single work package involving only some parties (or in some cases only one party) in the Work Package

Working and writing group: ESM group (Inez Myin Germeys, Eva Velthorst, Barnaby Nelson, Uli Reininghaus, Jim van Os) and WP5 author group.

Work Packages involved: WP5

EU-GEI Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated:

Objectives (scientific background, hypothesis, methods, and expected results):

Background and aims
Disturbed sleep is a known and prevalent characteristic of patients with psychosis. Insomnia, the inability to fall and stay asleep, affects the vast majority of individuals diagnosed with schizophrenia [1]. Profound abnormalities in sleep architecture [2] and circadian rhythms [3] have been identified. Sleep disruptions may represent an early clinical characteristic for developing psychosis in high risk populations [4]. As disordered sleep seems to be associated with increased negative and positive symptoms, a role for sleep in the pathophysiology of psychotic disorders has been proposed [1, 5, 6].
Although sleep may be a pivotal factor in the development and course of psychosis, the (bi-)directional associations between sleep and daytime psychotic experiences, and the transition to first-onset psychosis in at-risk populations, have gained very little research attention [7]. The EU-GEI WP5 Experience Sampling Method (ESM) dataset provides the unique opportunity to investigate the day-to-day associations between (i) previous night's sleep and subsequent daytime psychotic experiences and (ii) daytime psychotic experiences and subsequent night time sleep, possibly shedding light on underlying mechanisms linking sleep and psychosis. Combined with the possibility to test for the association between baseline sleep disturbance and follow-up transition rate to psychosis in an ultra-high-risk population, this could yield unprecedented insights into the link between sleep and psychosis.

This publication proposal has the following specific aims:

(1) Characterising self-reported sleep variables (sleep timing, sleep quality, sleep onset latency, number of awakenings) in UHR young people in relation to current psychopathology (specifically, in relation to mood symptoms) and in comparison to healthy controls

(2) Specifying the *day-to-day* associations between subjective sleep and subtle psychotic experiences during the day in UHR adolescents. Does sleep during the night impact on psychotic experiences during the day or vice versa?
(3) Investigating if baseline sleep disturbances predicts (i) the transition to a first-episode psychosis or (ii) the severity of symptoms at 12 and 24 months follow-up.

Methods

The sample will comprise 60 UHR patients aged 15-24 and xx healthy, age matched control participants who are taking part in a naturalistic prospective multi-centre study (EU-GEI). At baseline, these participants will undergo a 6-day study protocol using the Experience Sampling Method (ESM). ESM assesses participants' experiences prospectively and repeatedly (10x times during the day) in the flow of daily life, allowing to assess subtle psychotic experiences in everyday life (i.e. 'I feel unreal', 'I hear things that aren't really there'). Integrated in the experience sampling protocol will be a daily sleep diary, assessing subjective sleep variables (timing, quality, onset latency, number of awakenings) prospectively every morning upon awakening. Psychopathology (CAARMS, SCID-I, SPI-A, SANS, BPRS, MADRS) will be assessed during baseline, after 12 months, and 24 months (or, if transition to fist-episode psychosis took place, at 12 months and 24 months post-transition).

The following analyses will be performed:

(1) Using multilevel regression analyses, sleep characteristics in the UHR adolescents will be analysed in relation to current levels/severity of psychopathology. It will be investigated if diagnostic status (UHR/control) will predict self-reported sleep measures.
(2) Using multilevel regression analyses, the day-to-day associations between sleep and psychotic experiences will be investigated with (i) previous night's sleep as predictor and subsequent daytime psychotic experiences as outcome, and (ii) daytime psychotic experiences as predictor and subsequent sleep as outcome in lagged analyses.
(3) Using multilevel (logistic) regression and survival analysis, it will be investigated if poor self-reported sleep at baseline predicts (i) transition to psychosis, (ii) severity /level of psychopathology.

Expected results

(1) Self-reported sleep will be poorer (i.e. worse sleep quality, later sleep timing, longer sleep latency, higher number of awakenings) when psychopathology is higher. Self-reported sleep will be poorer in the group of UHR patients compared to the healthy control group.
(2) Self-reported sleep will predict next-day psychotic experiences (negative association: worse sleep is associated with more psychotic experiences the next day, especially for the sleep variable 'subjective sleep quality'). Psychotic experiences during the next day will predict subsequent sleep. Analyses are explorative as to the question which direction of the association will be stronger.
(3) Poor self-reported sleep as baseline will predict transition to psychosis and higher levels of psychopathology.

The investigation of (i) general sleep patterns in relation to psychopathology in an ultra-high-risk sample, (ii) the day-to-day associations between sleep and everyday psychotic experiences, (iii) the investigation of the directions of these associations (i.e. what impacts what), as well as (iv) the role of sleep in the transition to psychosis, may yield unprecedented insights into the exact role sleep plays in the pathophysiology of psychosis. Adolescence is associated with profound changes in sleep patterns as well as with the onset of psychosis. If sleep disturbances indeed precede the transition to psychosis or precede an aggravation of psychopathology, new routes to preventive interventions can be provided.

Synopsis for EU-GEI WP5 Publication

Data needed for the study: (please list the EU-GEI WP5 instruments)

Demographics
SPI-A (baseline)
CAARMS+ (baseline and follow up)
SCID (baseline and follow up)
SANS (baseline and follow up)
BPRS (baseline and follow up)
MADRS (baseline and follow up)
ESM data (baseline)
Transition status

Plan for statistical analysis (overall strategy):

ESM data have a multilevel structure, such that multiple observations are nested within subjects. Linear mixed models will therefore be used to control for within-subject clustering of multiple observations. In a two-level model, multiple observations (level-1) will be treated as nested within subjects (level-2). First, models will be fitted with group status (UHR/control) as independent variable and 'perceived sleep' as outcome. Second, models will be fitted with 'psychotic experience' as the independent variable and subjective 'sleep' variables as the dependent variable, adjusting for potential confounding factors (UHR patients only). Subsequently, lagged models will be fitted with 'sleep' as independent variable and 'psychotic experience' as the dependent variable, adjusting for potential confounding factors (UHR patients only). Second, multilevel models will be fitted with baseline sleep as independent variable and symptom severity during follow-up as dependent variable, again controlling for potential confounding factors (UHR patients). Survival analysis will also be used to examine the relationship between the baseline measures (sleep disturbance) and rate of transition to psychotic disorder (UHR patients).

Other analyses/methods:
N/A

Involvement of external Parties (non EU-GEI):

Nil.

IPR check (Intellectual property rights):
N/A

Timeframe:

Start date: Date of completion of ESM data collection in Amsterdam, London, and Melbourne.
Month 2: Literature search; obtaining, merging, checking, cleaning of data.
Month 4: Completion of statistical analysis and first draft of manuscript.
Month 6: Manuscript submission.

Additional comments:
Please note that the non-ESM data requested will only be analysed in relation to the ESM data.

References

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