BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019059
Article Type:	Protocol
Date Submitted by the Author:	14-Aug-2017
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY, Schizophrenia & psychotic disorders < PSYCHIATRY, MENTAL HEALTH

Title: A study protocol for a prospective cohort study examining the predictive potential of dynamic symptom networks for the onset and progression of psychosis: The Mapping Individual Routes of Risk and Resilience (Mirorr) study

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Abstract (295 words)

Introduction: Our current ability to predict the course and outcome of early psychotic symptoms is limited, hampering timely treatment. To improve our understanding of the development of psychosis, a different approach to psychopathology may be productive. We propose to re-conceptualize psychopathology from a network perspective, according to which symptoms act as a dynamic, interconnected system, impacting on each other over time and across diagnostic boundaries to form symptom networks. Adopting this network approach, the Mapping Individual Routes of Risk and Resilience (Mirorr) study aims to determine whether characteristics of symptom networks can predict illness course and outcome of early psychotic symptoms.

Methods and analysis: The sample consists of N=100 participants aged 18-35 years, divided into four subgroups (N=4x25) with increasing levels of severity of psychopathology, representing successive stages of clinical progression. Individuals representing the initial stage have a relatively low expression of psychotic experiences (general population), whereas individuals representing the end stage are help-seeking and display a psychometric expression of psychosis, putting them at ultra-high risk for transition to psychotic disorder. At baseline and 1-year follow-up, participants report their symptoms, affective states and experiences for three consecutive months in short, daily questionnaires on their smartphone, which will be used to map individual networks. Network parameters, including the strength and directionality of symptom connections and centrality indices, will be estimated, and associated to individual differences in and within-individual progression through stages of clinical severity and functioning over the next three years.

Ethics and dissemination: The study has been approved by the local medical ethical committee (ABR no. NL52974.042.15). The results of the study will be published in (inter)national peer-reviewed journals, presented at research, clinical and general public conferences. The results will assist in improving and fine-tuning dynamic models of psychopathology, stimulating both clinical and scientific progress.

Trial registration:

Netherlands Trial Register NTR6205, Registered 27 October 2016.

http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6205

Strengths and limitations of this study:

- One of the first studies examining the predictive potential of dynamic symptoms networks for the onset and progression of psychopathology
- The study design allows considering within- and between-individual variation in symptomatology, both at the micro (day) and macro (year) level
- A developmental, transdiagnostic approach is adopted; outcome measures include clinical stage, diagnosis, symptoms of a broad range of disorders and functioning
- With three yearly follow-ups, we may not capture all transitions to psychosis
- The exploratory nature of the study warrants replication of the findings

Words (main text): 4833

Introduction

Psychotic disorders are among the most severe mental disorders in terms of individual and societal impact [1, 2]. Therefore, early detection and intervention in psychosis should be highly prioritized [3], which is increasingly acknowledged [4]. Psychosis is currently conceptualized as a continuum of psychotic severity, encompassing both subclinical and clinical expression [5]. As such, psychotic symptoms do not only present in the context of psychotic disorders, but also across other, non-psychotic disorders [6, 7].

Current diagnostic systems in psychiatry are challenged by issues such as high levels of comorbidity, clinical heterogeneity, non-specific treatment effects, and lack of diagnosis-specific biological/ cognitive markers [8-12]. Despite this, traditional diagnoses still dominate psychiatric research, hampering scientific progress. These diagnoses are based on clinical presentation of adults with long-established illness [13], and classify individuals according to distinct diagnostic labels [8] (e.g. schizophrenia or major depressive disorder). However, it is increasingly acknowledged that psychopathology is expressed dimensionally, representing a quantitative as well as qualitative deviations from mental health [8, 14-19]. In addition, it is increasingly accepted that mental disorders do not emerge fully formed in adulthood but evolve gradually, often manifesting for the first time already in adolescence [20, 21].

A model that was designed to capture this continuity of both severity and time is the clinical staging model [22, 23]. This model describes psychopathology as ranging, through subsequent but qualitatively different stages, from increased risk of mental illness at the lowest level through progressive stages of severity, resulting in separable but overlapping syndromes at the highest

levels [24, 25]. Stage 0 represents individuals at increased risk without symptoms; Stage 1a represents 'help-seeking' individuals with mild, non-specific symptoms; Stage 1b represents individuals with an 'attenuated syndrome', with moderate but subthreshold symptoms and moderate functional decline; Stage 2 holds individuals with a first episode of a clinical, 'discrete', disorder; Stage 3 holds individuals with persistent or recurrent illness [13, 22, 23] and Stage 4 represents individuals with chronic illness. This clinical staging model further hypothesizes that psychopathological expression is more multi-dimensional, non-specific and more susceptible to intervention in early stages and becomes more crystallized, disorder specific and treatment-resistant in later stages [25]. This model offers a theoretical representation that seems to fit better to the true nature and development of psychopathology [9-11, 26], and hence may improve diagnostic accuracy. First investigations of the model seem promising, but more empirical research is needed [27]. It has been developed most extensively in the context of psychosis [23, 25, 28], but needs thorough empirical validation, since many questions still remain, e.g. about what drives progression through subsequent stages and how the thresholds between the stages should be defined exactly.

The expression and development of early psychotic symptoms are highly variable [29-32] and difficult to predict [33, 34]. One reason for this is that many studies so far have focused on early psychotic symptoms as specific predictors of later schizophrenia. However, this approach may be too narrow [25, 31, 35] because early psychotic symptoms are often transitory [36-38], also occur in the context of [6, 7, 39-41] and predict other mental disorders [33, 36, 42, 43], and vice versa [44-46]. High levels of comorbidity [47] and overlap of risk factors [48-51] also challenge the assumed independence of psychosis from other symptom domains. In addition, the

information that is used to predict course and outcome is often based on cross-sectional assessment of symptoms and comparisons are often made at the group level. However, symptoms can vary substantially over time, both over short (i.e. days) and long intervals (months, years), within one individual, and can also cross diagnostic borders [52]. This means that the clinical picture can change, particularly in the early phase of a disorder [25]. These characteristics of psychopathology suggest that the ´static´ model prediction may not be fit for the purpose. This is reflected in the modest accuracy and replicability of static prediction models in the psychosis prediction field [53-55].

The Mirorr study

The above-mentioned challenges may be overcome by taking a different approach towards the conceptualization of psychopathology, its measurement and the way we model it. By taking a more transdiagnostic approach, incorporating symptoms and experiences from multiple (psychotic and non-psychotic) domains, the narrow focus on the sole dimension of psychosis can be broadened. By modelling individual patterns of symptom patterns over time, a more developmental as well as a more personalized approach can be taken that, in addition, builds on a more detailed inventory of symptomatology compared to baseline (cross-sectional) assessment scores. Modelling the interconnectivity between symptoms by mapping individual symptom networks and patterns of co-occurrence in and over time could provide us with a better idea of how psychopathology develops and may give us clues on what processes may drive progression through subsequent clinical stages [56, 57]. To investigate these aspects, we designed the *Mapping Individual Routes of Risk and Resilience* (Mirorr) study.

Aims and hypotheses

With the Mirorr study, we aim to investigate the hypothesis of dynamic symptom networks as the basis of psychopathology in general and psychosis in particular. Furthermore, we aim to investigate the additional hypothesis of symptom networks as markers/indicators of progression of illness through successive clinical stages. Taking a broader, multidimensional and process-oriented approach, we will examine how symptoms of multiple domains influence each other over time and across diagnostic boundaries, in interaction with environmental factors. More specifically, we hypothesize that different clinical stages will be characterized by different symptom networks. In addition, we expect that characteristics of these networks can predict progression through clinical stages. We will explore the predictive potential of several characteristics, such as the strength and directionality of symptom connections (see Figure 1) and centrality indices (information about the position of a symptom in the network).

The Mirorr study is unique in its design and in its attempt to (i) bring together a network approach to psychopathology and the clinical staging model, (ii) take a broader perspective on mental illness by (a) taking a transdiagnostic approach towards symptomatology and (b) defining outcome in more broadly in the context of clinical staging (incorporating both clinical and functional outcomes), and (iii) modelling individual symptom networks over time by using time-series data, enabling us to model more personalized pathways of psychopathological development.

A network approach to psychopathology

A focus on dynamic symptom networks requires an innovative approach to psychopathology. One of the currently promising alternative approaches comes from network theory. From this network perspective, psychopathology, at a phenomenological level, is hypothesized to result from interactions between symptoms [11, 58, 59]. Mental disorders are thus represented by sets of symptoms, connected in networks by causal relations [11, 58] (see also Figure 1). These networks are dynamic and capture reciprocal influences between symptoms over time (e.g., feedback loops). Importantly, symptoms are acknowledged as causal factors in psychopathological development: one symptom (e.g., anxiety) can cause another (e.g., paranoia). This is in sharp contrast with current dominant models that represent symptoms as independent indicators of underlying, latent constructs (e.g., schizophrenia). As stress is important in the development of psychosis [60, 61], the sensitivity of symptom networks to risk-enhancing (trauma) and risk-reducing (coping, social support) factors [62, 63] also needs attention. The network approach has been successfully applied in other fields [64, 65], but is relatively novel in psychiatry, where it has been investigated mainly in common mental disorders [66], but not psychosis.

Outcome measures

Traditionally, research in the field of psychosis focuses mostly on transition from clinical high risk to a first episode of psychosis [67]. However, there is growing awareness that this may be arbitrary, especially in the context of a staging model that acknowledges expression of illness along a much broader severity spectrum. In addition, functional outcome is becoming more and more an important outcome of interest, as it has been shown that both clinical and functional outcome are important but not always congruent [68-70]. Working from a clinical staging

perspective, important outcomes to investigate include therefore progression through clinical stages, functioning and need for care.

Please insert Figure 1 here.

Objectives

Primary Objective:

To investigate whether symptom networks can characterize different clinical stages and predict progression through subsequent stages, and whether there is a unique role of psychotic symptoms within these networks in a sample of young adults (18-35 years) with increased risk for psychosis. For this purpose, we examine both within-individual changes and between-individual differences in symptom networks and clinical stage.

Secondary Objectives:

1) To identify symptom networks that predict development of mental illness more accurately than current models that are based on a cross-sectional assessment of symptom severity, which have limited predictive accuracy;

2) To examine how risk and resilience factors for stress influence symptom networks. Examples of risk factors are daily stress and early trauma; examples of resilience factors are coping strategies, social support, physical activity and the experience of positive affect.

Methods and analysis

Study design

This study combines idiographic (within-person) and nomothetic (between-person) observational study designs. The nomothetic aspect of the study is captured by questionnaire and interview data at baseline and three yearly follow measurement waves. Among other things, symptomatology, functioning and need for care will be assessed (outcome measures), as well as risk and protective factors. The idiographic aspect is captured by diary assessments at baseline and the first follow-up wave. During the diary periods, participants will complete a diary questionnaire daily for a period of 90 days on their smartphone, regarding symptoms, emotions, functioning and stress. These diary data are used to map individual symptom networks. For the second diary period, participants can also opt to keep continuing the questionnaire follow-ups, but not have a second diary period. A flowchart of the study is presented in Figure 2.

Please insert Figure 2 here.

Study population

The total sample comprises of 175 individuals of 18-35 years, whereof 100 will enter the main study (i.e. the daily diary study and the yearly follow-ups). For the main study, there will be four subsamples, all n=25 (Figure 3) with each subgroup having an increasingly more severe psychopathological level and thus representing subsequent clinical stages. For subsample 1 (lowest level of psychopathology and thus lowest clinical stage), 100 individuals will be randomly selected from the general population in the North of the Netherlands and administered the Community Assessment of Psychic Experiences (CAPE) [71]. Of all the respondents who meet the inclusion and exclusion criteria of the study, the highest scoring quartile will be

included in the main study. For subsamples 2-4, individuals will be recruited from mental health care institutions in the four Northern provinces in The Netherlands. For all individuals who are referred to mental health care, psychotic symptoms are routinely screened by means of, among other things, the Prodromal Questionnaire (PQ) [72]. If the score on the PQ is 6 or higher, the Comprehensive Assessment of At Risk Mental State (CAARMS) [73] is administered as well. With these scores it is determined for which subsample (2-4, explained below) eligible subjects will be recruited, where a higher subsample indicates higher levels of psychopathology.

Please insert Figure 3 here.

In order to be eligible to participate in the study, subjects must meet all of the following criteria: 1) age between 18 and 35 years, 2) read and speak Dutch fluently, 3) capable of following the research procedures, 4) provide Informed Consent. In addition, participants of subsample 1 should *not* be in clinical care for mental health at the moment of screening. In contrast, participants of subsample 2-4 *should* currently be in clinical care for mental health. In addition, participants of subsample 2 should have mild, non-psychotic psychopathology, as evidenced by a score below 6 on the PQ, participants of subsample 3 should have mild psychopathology including subclinical psychotic symptoms, as evidenced by a score of or above 6 on the PQ, but are not at ultra-high risk (UHR) for psychosis, as indexed by the CAARMS. Finally, participants of subsample 4 should be at UHR for psychosis, as indexed by the CAARMS. Exclusions criteria are: 1) a history of or current psychotic episode, according to the Diagnostic and Statistical manual of Mental Disorders-IV (DSM-IV) criteria; 2) significant hearing or visual problems impairments; 3) pregnancy, as stated on a general health questionnaire.

Procedure

Recruitment

To recruit subsample 1, the study will be announced at several university sites, public places in Groningen, and social media (start recruitment: September 2015). Interested individuals can contact the researchers by phone or e-mail for more information. They will then be sent an information letter, flyer, informed consent form and the initial screenings questionnaires. After receiving the completed screening questionnaires and informed consent forms, the 25 (out of 100) individuals with the highest CAPE scores will be invited to participate in the main study (first inclusion: December 2015). For subsample 2-4, individuals will be recruited from mental health care institutions in four northern Dutch provinces (first inclusion: April 2016). To which subsample they will be recruited is determined using the instruments described under study population. For these sites where patients give their consent for receiving information about ongoing research projects, a package containing detailed information on the study (information letter and flyer), along with screening questionnaires and an informed consent form will be send to potential participants. Interested individuals can fill out and return requested forms (including informed consent form). After receiving the requested forms, an individual's therapist will be consulted about several exclusion criteria. For these sites where participants do not give consent in advance, the individual's clinical worker will be provided a package containing detailed information on the study (information letter and flyer), along with screening questionnaires and an informed consent form. The clinical worker will pre-screen his/her client on the exclusion criteria of the study and hand over the package if he/she fits the profile of the study. Study

participants can continue their therapy and medical treatment as usual; they will be asked to register any changes in medication or treatment during the daily ambulatory assessments.

Screening

The information package that interested individuals receive contains an information letter, two screening questionnaires and an informed consent form. All potential participants can ask questions before completing informed consent form or the screening questionnaires. As mentioned in the information letter, in case subjects should decide to participate, they should fill out and send back these questionnaires and the informed consent form. This consent form covers the baseline ambulatory assessment period and the yearly follow-up assessments (three in total). On this consent form permission will be asked to re-invite subjects for the follow-up ambulatory assessment period, for which they have to complete a separate consent form (one year later). Also, permission will be asked to use data from the psychiatric case register of the North of the Netherlands. The first screening questionnaire is a screening questionnaire on general health, containing questions on demographics, health complaints (such as visual or hearing impairments), pregnancy, drug and alcohol use, medication use, and mental health problems. This will be used to screen on exclusion criteria. The second screening questionnaire is the CAPE. This instrument is used to screen individuals recruited from the general population (subsample 1) on psychotic experiences but will be administered to all participants to enable group comparisons on the level of subclinical psychotic experiences. The highest scoring quartile (n=25) will subsequently be included in the main study. Subjects will have one week to decide about participation.

Baseline interview and ambulatory assessments (year one)

If subjects are eligible to enter the study and agree to participate, they will be invited (by telephone or e-mail) for an introduction interview at the University Medical Centre Groningen. A few days before the interview, self-report questionnaires will be administered via email (see data management for more information). The questionnaires assess symptomatology, functioning, clinical stage, and factors of risk and resilience. During the interview, the study will be explained to them in detail and a diagnostic psychiatric interview will be held. If in an exceptional case the participant does not possess a smartphone, this will be provided to the participant during the study period. An appointment for an end-of-study interview will be planned. Also, the participants will be asked to designate suitable moments at which the researcher can call him/her to inquire on the progression of the study and to help with any problems the participant may experience.

The participants then start completing the electronic daily diary for three months. Every evening, they receive a text message with a link which directs them to a web-based diary questionnaire in a secure environment. Measurements are always in the evening, asking about the past day; exact times can vary per person (but not per day) and are fixed according to the participant's wishes. However, *all* participants have 24 hours between each measurement point. For example, participant A will always receive her text message at 22.00 and participant B always at 21.15. A window of one and a half hour will be allowed to fill in the diary, and reminder messages will be send every half hour. Short questions will be presented on sequential screens, which are mainly answered using visual analogue scales. During the research period, participants are also provided a paper log, in which they can note any unusual events, start of or changes in medication use and

problems they encounter with the research procedures. The researchers will telephone the participants six times during the study period (every other week), to motivate the participant, answer questions about the study procedures and provide technical help. They will also be available by telephone and e-mail if participants need help at other moments.

During the end-of-ambulatory-assessment (3 months after baseline) interview participants will fill out an online questionnaire battery once more, and report on any changes in medical treatment. Furthermore, they will also be asked to comment on the data collection and the study in general. We will use this information to check whether the study affected their thoughts and behaviours in any way, whether there had been special events that might have affected the data collected.

Follow-up assessments

One, two and three years after baseline, all participants will receive questionnaires about functioning and clinical stage via email. The participants will be able to fill these in at home. Shortly after filling in the questionnaires, participants will be interviewed by telephone or face-to-face at one of our research facilities, depending on their preferences, to establish the presence/absence of psychiatric disorders with a diagnostic interview. In addition, to distinguish individuals in clinical stage 1a from individuals in clinical stage 1b (all individuals with a score of 6 or higher on the PQ-16), data from the CAARMS interview is needed. Participants will be reminded about the follow-up assessments a few weeks before the actual follow-up by means of an information letter.

Follow-up ambulatory assessment period (year two)

In the aforementioned information letter, participants will also read information about a second ambulatory assessment period that they can enrol in. If they are interested, they are invited for another introduction interview (given that they still fulfil the in- and exclusion criteria as evidenced by their answers to an online version of a general health questionnaire). This interview is similar to the introduction interview at baseline (i.e., questionnaire battery and procedures). An exception is that questionnaires about symptomatology, functioning and clinical stage will not be administered, because they have been covered already by the usual follow-up assessments. Participants then start their second three-month period of ambulatory assessments one year after the first diary period. The end-of-ambulatory-assessment interview will take place, again with similar questionnaires to the one held at baseline.

Instruments

A complete overview of the instruments used throughout the study is presented in Table 1.

Please insert Table 1 here.

Diary measures

The items assessed in the daily questionnaires will be used to model individual networks of symptoms, experiences and emotions. Items included in the dairy questionnaires were chosen from a transdiagnostic perspective and cover a broad range of feelings and experiences that are characteristic for (subclinical) psychotic experiences, depression, anxiety, mania, obsessive compulsive behaviour and anger. These disorders are known for the co-occurrence of psychotic

symptoms [6, 7] and comorbidity [47]. For the complete item list, see Additional file 1, Table S1.

Positive psychotic experiences can be divided into five categories, namely paranoia, delusions, hallucinations, megalomania, and paranormal beliefs [74]. Because paranormal beliefs are often stable over time, we will include items covering the first four categories. Negative symptoms of psychosis will be covered by items about flattened affect (e.g., anhedonia, low motivation, social withdrawal), which resemble closely the negative symptoms of the CAPE. Most items are adopted from previous ESM studies [75-77], and all items are adapted for daily use.

Symptoms of depression will be measured using items that correspond closely to the patient health questionnaire (PHQ-9) [78], a self-administered questionnaire for screening and measuring the severity of depression. Anxiety symptoms will be measured using items that correspond closely to the Hospital Anxiety and Depression Scales – Anxiety (HADS-A) [79]. Mania, obsessive compulsive behaviour and anger are measured with items that correspond closely to items from the DSM-V – screener for the corresponding clinical disorders [80].

Positive and negative mood states over the past day will be measured with 12 items from the circumplex model of affect [81, 82]. Momentary affect will be measured with an item for valence ("I feel unpleasant – pleasant") and activation ("I feel aroused/activated – quiet/still") at the beginning of each diary entry. Other items cover sleep, daily activities and situations that may influence psychiatric symptoms, such as positive and negative events, social interactions, coping behaviour, physical activity and drug use.

Follow-up measures

Important outcomes that are linked to the above described network characteristics are (progression through) clinical stages, functioning and need for care. Progression through clinical stages will be assessed with the PQ-16, the CAPE and the CAARMS, the Symptom Check List (SCL-90) [83] and the Schedules for Clinical Assessment in Neuropsychiatry, short version (mini-SCAN) [84]. Social functioning will be assessed using the Groningse Vragenlijst voor Sociaal Gedrag (GVSG-45) [85] and the Flourishing Scale [86]. Need for care will be assessed using self-reported information on care use. Additionally, need for care will be assessed by linking data from the psychiatric case registry to our sample when approved by the participant (as stated on the informed consent form). Specifically, the frequency and type of care use throughout the study period will be obtained.

Assessments pre- and post-daily diary period(s)

Before and after the daily diary assessments, several questionnaires will be administered to assess symptomatology, functioning and several risk and resilience factors. Psychotic symptoms will be assessed with the CAPE; depression and anxiety symptoms with the Depression Anxiety and Stress Scale (DASS) [87]; mania symptoms with the Altman Self-Rating Mania Scale (ASRM-NL) [88], social support with the Social Support List (SLL) [89]; resilience with the Brief Resilience Scale (BRS) [90] and coping style with the Utrechtse Coping Lijst (UCL) [91]. Furthermore, physical activity levels will be tracked with an accelerometer, the ActiCal® (Respironics, Bend, OR, USA), during the first two weeks of the second diary period. Output of

this instrument will be presented as Energy Expenditure and Metabolic Equivalent of Task. The physical activity measurements are added to serve as a pilot study, and are not obligatory.

At baseline, sleep habits will be assessed with the Munich Chronotype Questionnaire (MCTQ) [92] to optimize the diary assessment process. Also, potential confounders such as smoking, alcohol/drug consumption, socio-economic status, Body Mass Index will be registered by means of a general health questionnaire. In addition, stressful life events will be assessed, using the list of threatening experiences [93]. Finally, pertaining to subgroup 4 only, social cognition will be assessed using the Faux Pas Task [94] and bonding with parents will be assessed with the Inventory of Parent and Peer Attachment (IPPA) [95, 96]. These factors may be of importance in determining a transition from an UHR status to psychosis.

Data analysis plan

To map individual symptom networks of day-to-day symptom levels, multivariate time-series analysis will be employed on each individual's time series data. Specifically, vector autoregression (VAR) models will be applied [97]. These models are particularly suited for investigating the temporal dynamics between two or more variables. The resulting associations between symptoms will subsequently be presented as networks, and network parameters will be estimated. These include (but are not limited to) the strength and directionality of symptom connections (see Figure 1) and centrality indices (information about the position of a symptom in the network). Next, symptom networks will be compared (i) across different subgroups of severity and (ii) when the second diary period is completed, within each individual.

In addition, a data-driven approach will be used to identify individuals with similar symptom network characteristics by (1) qualitative network comparison, (2) quantitative comparison of centrality indices [98, 99], and (3) longitudinal mixture models [100]. These subgroups will then be compared on their levels of symptomatology and functioning and on course of symptomatology over time. Furthermore, the predictive value of the network parameters will be compared to the predictive value of usual predictors of illness course, namely cross-sectionally assessed level of (subclinical) psychotic pathology. Specifically, sensitivity and specificity of these network characteristics can be compared to sensitivity and specificity of baseline subclinical levels of psychotic symptoms (CAPE) and general psychopathology (SCL-90). Finally, risk and resilience factors, such as stressful events, social interactions, physical activity, coping and resilience, may also influence symptoms and, importantly, their dynamics in the network, but may do so differently in individuals with good or poor clinical and functional outcome. The role of these factors will be addressed by including them in individual network analyses to examine their direct and indirect impact on symptomatology and each other.
To control for potential confounding effects of demographic factors, such as sex, age and social economic status, these variables will be added as covariates to all group level analyses.

Based on previous work [101, 102], we expect no more than 10% missing data. Missing values will be imputed with expectation-maximization imputation, following special recommendations for time-series datasets [103]. A (two-sided) p-value of 0.05 is applied for statistical testing.

Sample size and power

Within-person analyses: constructing individual symptom networks

Exact sample size calculations are not possible in studies using VAR, as it is typically unclear in such studies what effect size can be expected. This is because the direction of causality and the number of lagged influences in the system under investigation are usually unknown and bidirectional and feedback effects can be present as well [97]. However, as previous work from our group [101, 104, 105] and work of others [106] suggests, 60-90 measurements suffice to reliably identify reciprocal associations between multiple variables.

Between-person analyses: associating symptom networks to clinical stage

In the between-person analyses, the data have a multilevel structure. Therefore, the unilevel equivalent of the multilevel sample size [107] was taken to calculate the power, assuming a conservative intraclass-correlation of 0.8. Assuming differences of 0.05 in mean coefficients (s.d. = 0.07) between the different groups [108], the proposed study has a power of 0.8 (to detect significant differences at $p<0.05$). Subgroups of N=25 are large enough to take into account effects of several covariates [109].

Ethics and dissemination

This study has been approved by the medical ethical committee of the University Medical Centre Groningen (UMCG), Groningen, The Netherlands (registration number MEC no. 2015/159, ABR no. NL52974.042.15). The study will be conducted in accordance with the Helsinki Declaration, meaning that participation is voluntary and written informed consent will be obtained.

An online outcome monitoring system, called RoQua (www.roqua.nl) is used for data collection and data storage, to which only designated researchers have access via the use of passwords combined with google authentication. Participants have access to the questionnaires via a link in their e-mail inbox. The safety of this system is guaranteed by the UMCG (an 'In Control Statement' is available on request). Data management is also organized according to UMCG standards, including a strict separation of identifying patient data (name, date of birth etc.) and the anonymous datasets available for the researchers.

Data gathering was not completed when this manuscript was submitted. After the publication of this study's main results, the data obtained by this study will become available on reasonable request. Requests should be sent to j.t.w.wigman@umcg.nl with the topic name MIRORR data. The results of the study will be published in (inter)national peer-reviewed journals, presented at research, clinical and general public conferences.

Conclusion

Conceptualization of psychopathology in terms of (i) clinical staging (at macro level) and (ii) dynamic, individual symptom networks (at a more micro level), which is the purpose of this study, represents a promising avenue to tackle both scientific and clinical problems. Improving our understanding of the factors driving the development of psychopathology by investigating how symptoms influence each other will enhance our ability to identify valid phenotypes to predict onset of (psychotic) mental disorders and to link with other relevant information (e.g., genetic or endophenotypic variation). In addition, a better understanding of why psychotic symptoms can lead to a need for care in some, but resolve spontaneously in others, will help

mental health professionals to adequately recognize the early needs of individuals who are likely to develop mental illness or functional impairments.

Acknowledgements

We would like to thank the ROQUA team for their collaboration and for building and maintaining the smartphone web-based (diary) questionnaires. We are grateful to Laura Steenhuis, Roos Willemsen, Marike Fowler, Cornelie Glasbergen, Marijke Muller, Eliese van Deelen, Marion van Dijk, Sieberen Veenstra, Marietta Khachaturyan and Thirza Osinga for their contributions to the field work and data management. We thank Ernst Wit and Elske Bos for their conceptual and methodological input. Finally, we thank Rob Wanders and Ando Emerencia for their help with automating the personalized feedback procedure.

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Authors' contributions

JTWW conceived the study. JTWW and SHB designed and are executing the study and drafted the first versions of the manuscript. LW, PdJ, JvO, MCW helped conceptualize the study and provided overall supervision, SS contributed to the study design, specifically to the data gathering and data management part. All authors critically reviewed the manuscript, and collaborated in the discussion of the intellectual content of the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Netherlands Organization for Scientific Research (NWO) (Veni Dr. J.T.W. Wigman: no. 016.156.019). In addition, M. Wichers was supported by an H2020 European Research Council Consolidator Grant (ERC-CoG-2015, project 681466 – TRANS-ID). The funders had no role in the study design, data collection and analysis, decision to publish, or the preparation of the manuscript.

Competing interests

The authors declare that they have no competing interests.

796 **Tables**

797 Table 1. Overview of instruments.

Domain	Instrument	Method	Purpose	Time (min)	Screening	Diary pre (baseline)	Diary post	Follow-up 1	Diary pre	Diary post	Follow-up 2	Follow-up 3
					T0	T0	T0 (3m)	T1	T1	T1 (3m)	T2	T3
Demographics	Gen. Health	SR	Demogr, conf.	5	X				X‡			
	Vignette	INT	History psychosis	5	X**							
Psychosis	CAPE	SR	Psychotic Sx	6	X		X	X		X	X	X
	PQ	SR	Clinical stage	3		X†		X†			X†	X†
	CAARMS	INT	Clinical stage	30-90		X*†		X*†			X*†	X*†
Psychopathology	Mini-SCAN	INT	Diagnosis	30		X		X			X	X
	SCL-90	SR	Severity	20		X		X			X	X
	PsychCaseReg	REG	Care use	-		X		X			X	X
	Care use - extra	SR	Care use	1		X		X			X	X
	DASS	SR	Depress Anxiety Sx	3		X	X		X	X		
	ASRM	SR	Mania Sx	3		X	X		X	X		

Table 1. Continued.

Domain	Instrument	Method	Purpose	Time (min)	Scree-ning	Diary pre (baseline)	Diary post	Follow-up 1	Diary pre	Diary post	Follow-up 2	Follow-up 3
Social functio-ning	GVSG-45	SR	Social functioning	8		X		X			X	X
	Flourishing Sc	SR	Well-being	1		X		X			X	X
Risk & resil-ience	SSL	SR	Social support	7		X	X		X	X		
	IPPA	SR	Bonding	9		X#						
	BRS	SR	Resilience	2		X	X		X	X		
	UCL	SR	Coping	5		X	X		X	X		
	Brugha LTE	SR	Life events, trauma	4		X			X			
	MCTQ	SR	Sleep	3		X			X			
	Faux-Pas Task	INT	Social Cognition	5		X#						
	Actical®	SENS	Physical activity	-					X***			

Note. SR = Self-report, INT = Interview, REG = register, SENS = sensor Sx = symptoms, demogr = demographics, conf = confounders, depress = depression, T = measurement wave, m = months.

* Only administered when PQ score is 6 or higher.

** Only administered when there is a history of a psychiatric disorder according to the information on the General Health Questionnaire

*** Offered to participants as optional.

† Available as ROM data for all individuals in clinical care for mental health at each measurement wave.

‡ Send out several weeks before the daily diary period to screen on exclusion criteria

Administered only to subgroup 4

Figure titles and legends

Figure 1. Parameters of symptom networks.

Figure 2. Flowchart.

Note. Light grey area within blue dashed square indicates optional measurements.

Figure 3. Definition of subgroups.

Additional files

Additional file 1.docx

Title: Table S1. Diary items

Description: Original Dutch diary items and their translation to English

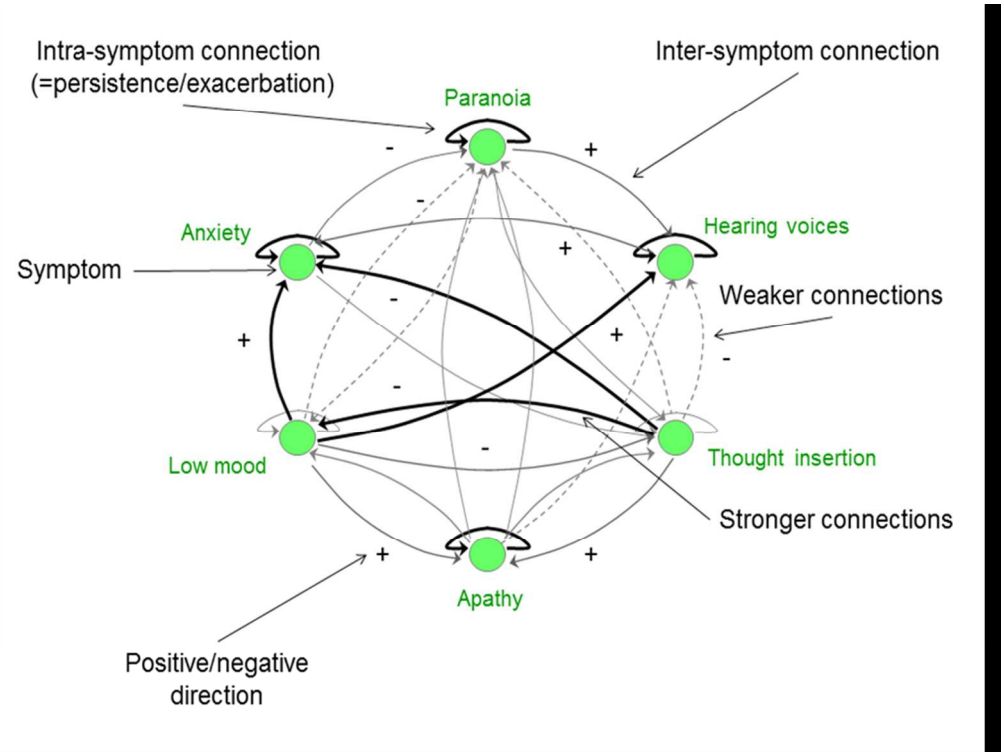
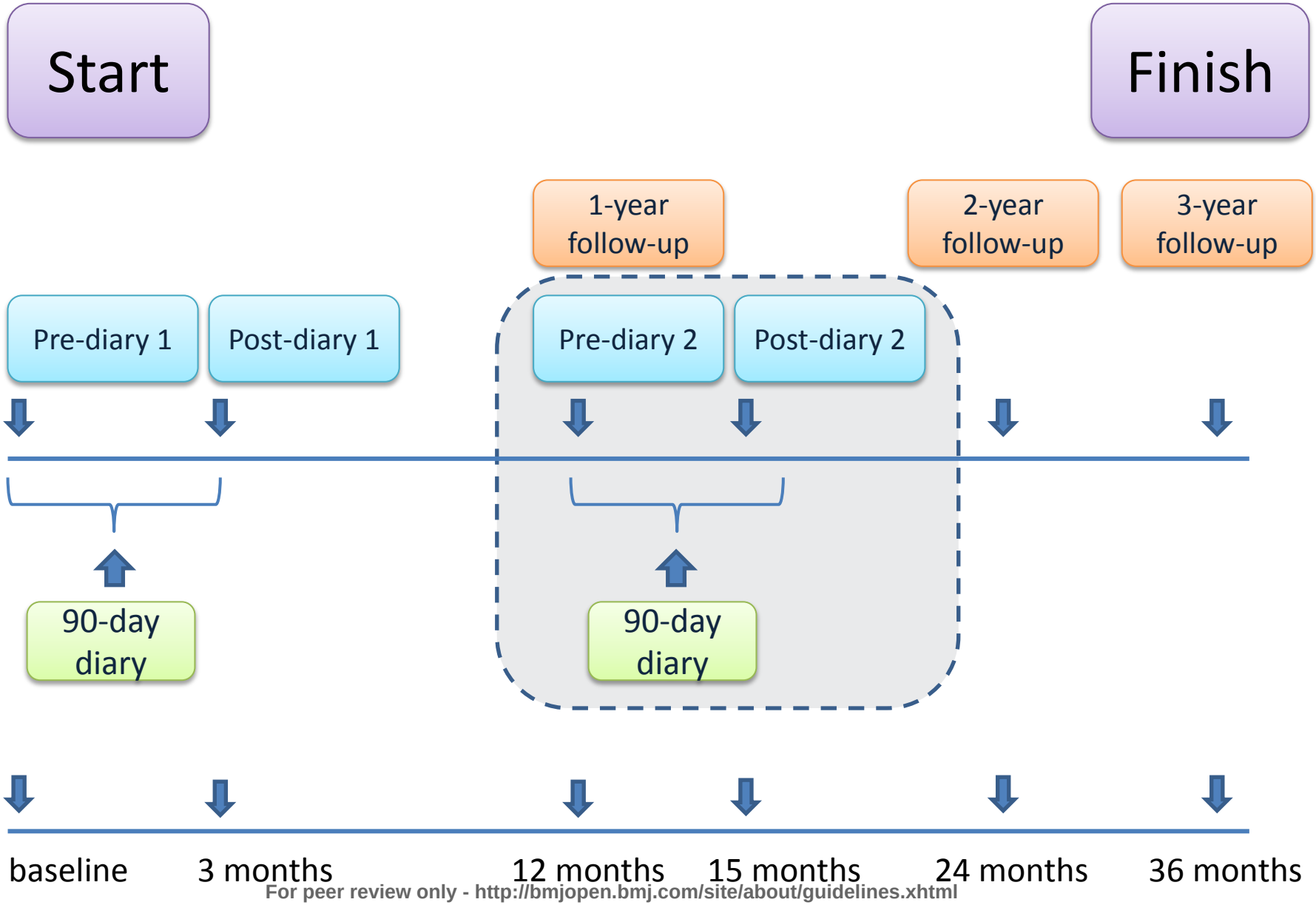
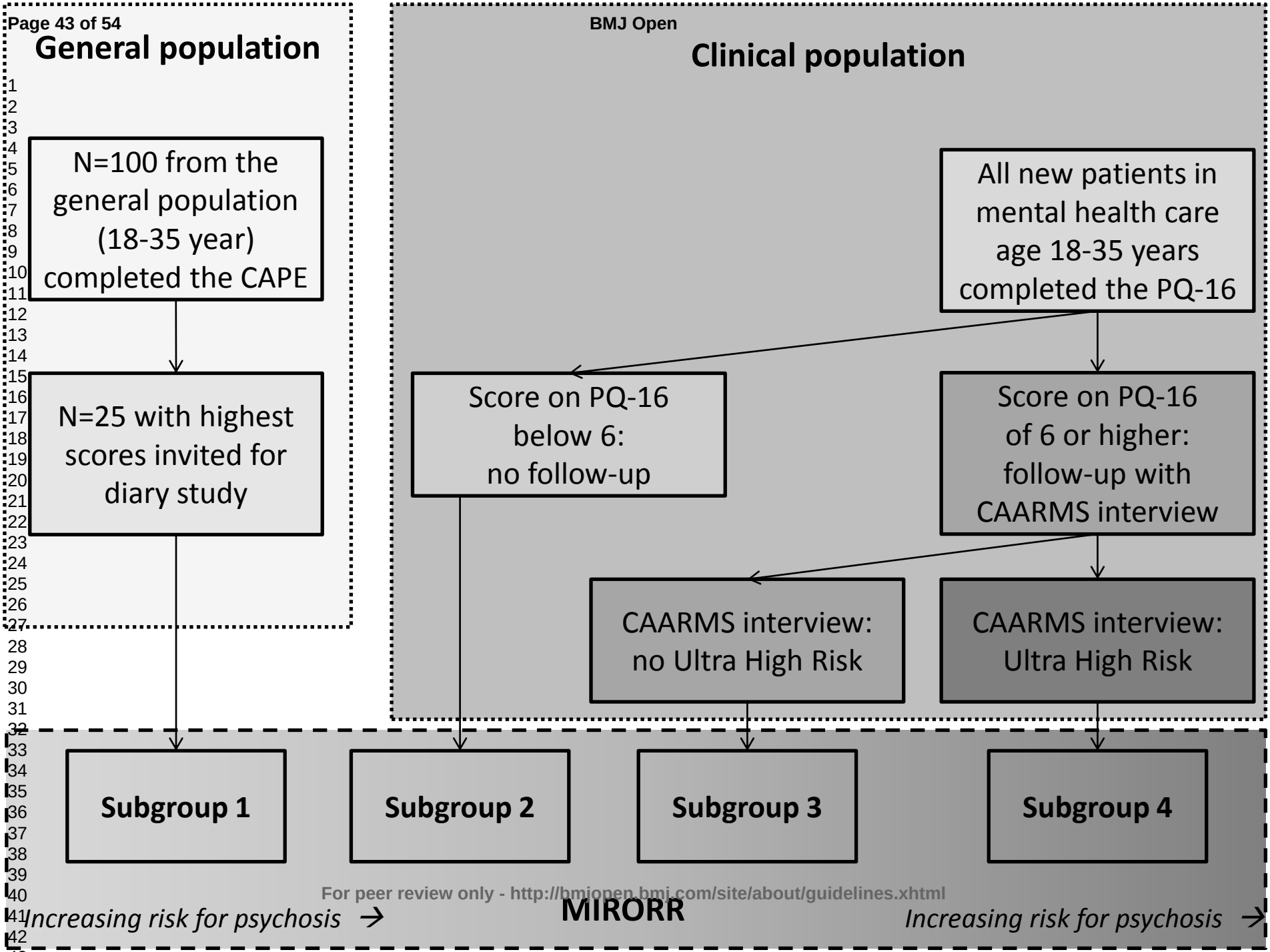


Figure 1. Parameters of symptom networks.

242x170mm (101 x 107 DPI)





Supplementary Table S1. Diary items.

Question	Dutch	Translation	Response range	Range	Description
1	Ik voel me nu	Right now, I feel	Very unpleasant – Very pleasant	0 - 100	Momentary affect
2	Ik voel me nu	Right now, I feel	Very restless / excited – Very quit/calm	0 - 100	Momentary affect
3	Op mijn beste moment van vandaag voelde ik mij	During my best moment of the day, I felt	Very unpleasant – Very pleasant	0 - 100	Momentary affect
4	Op mijn beste moment van vandaag voelde ik mij	During my best moment of the day, I felt	Very restless / excited – Very quit/calm	0 -100	Momentary affect
5	Wanneer was dit beste moment ongeveer? Ergens in de	Around when was this best moment? Somewhere in the	• Morning • Afternoon • Evening	1, 2, 3	Momentary affect
6	Op mijn slechtste moment van vandaag voelde ik mij	During my worst moment of the day, I felt	Very unpleasant – Very pleasant	0 - 100	Momentary affect
7	Op mijn slechtste moment van vandaag voelde ik mij	During my worst moment of the day, I felt	Very restless/ excited – Very quit/calm	0 -100	Momentary affect
8	Wanneer was dit slechtste moment ongeveer? Ergens in de	Around when was this worst moment? Somewhere in the	• Morning • Afternoon • Evening	1, 2, 3	Momentary affect
9	Heb je afgelopen nacht goed	Did you sleep well tonight?	Not at all – Very well	0 - 100	Sleep

	geslapen?				
10	Hoeveel uur heb je afgelopen nacht ongeveer geslapen?	About how many hours did you sleep tonight?	Hours, minutes	0 - 24	Sleep
11	Heb je vandaag overdag geslapen? (dutjes)	Did you sleep during the day today (naps)?	• No (skip to 13) • Yes	0 – 1	Sleep
12	Hoe lang in totaal?	How long in total did you sleep during the day today?	Hours, minutes	0 – 12	Sleep
Instruction	*Alle items gaan vanaf nu over de afgelopen dag (denk aan hoe je je vandaag gemiddeld voelde)*	*From now on, all items involve the past day (think about how you felt on average today)*			
13	Ik voelde me vandaag ontspannen	I felt relaxed today	Not at all – Very much	0 – 100	Positive deactivation
14	Ik voelde me vandaag kalm	I felt calm today	Not at all – Very much	0 – 100	Positive deactivation
15	Ik voelde me vandaag tevreden	I felt satisfied today	Not at all – Very much	0 – 100	Positive deactivation
16	Ik voelde me vandaag energiek	I felt energetic today	Not at all – Very much	0 – 100	Positive activation
17	Ik voelde me vandaag enthousiast	I felt enthusiastic today	Not at all – Very much	0 – 100	Positive activation
18	Ik voelde me vandaag opgewekt	I felt cheerful today	Not at all – Very much	0 – 100	Positive activation
19	Ik voelde me vandaag lusteloos	I felt apathetic today	Not at all – Very much	0 – 100	Negative deactivation
20	Ik voelde me vandaag moe	I felt tired today	Not at all – Very much	0 – 100	Negative deactivation
21	Ik voelde me	I felt down today	Not at all – Very much	0 – 100	Negative

	vandaag somber				deactivation
22	Ik voelde me vandaag angstig	I felt anxious today	Not at all – Very much	0 – 100	Negative activation
23	Ik voelde me vandaag onrustig	I felt restless today	Not at all – Very much	0 – 100	Negative activation
24	Ik voelde me vandaag prikkelbaar	I felt irritable today	Not at all – Very much	0 – 100	Negative activation
25	Ik voelde me vandaag geïrriteerd	I felt irritated today	Not at all – Very much	0 – 100	Irritation
26	Ik voelde me vandaag spraakzaam	I felt talkative today	Not at all – Very much	0 – 100	Spontaneity
27	Ik voelde me vandaag zelfverzekerd	I felt confident today	Not at all – Very much	0 – 100	Self confidence
28	Ik voelde me vandaag leeg/vlak	I felt empty today	Not at all – Very much	0 – 100	Flat affect / Anhedonia
29	Ik voelde me vandaag ongerust	I felt worried today	Not at all – Very much	0 – 100	Worrying
30	Ik voelde me vandaag erg speciaal	I felt very special today	Not at all – Very much	0 – 100	Delusions
31	Ik voelde me vandaag wantrouwig	I felt suspicious today	Not at all – Very much	0 – 100	Delusions
32	Ik had vandaag het gevoel te kort te schieten	Today I had the feeling of falling short	Not at all – Very much	0 – 100	Worthlessness
33	Ik kon vandaag aan wat op mijn pad kwam	Today I could handle what came my way	Not at all – Very much	0 – 100	Resilience
34	Ik kon me vandaag goed concentreren	I could concentrate well today	Not at all – Very much	0 – 100	Concentration

35	Ik vond mijn leven vandaag de moeite waard	I found my life was worthwhile today	Not at all – Very much	0 – 100	Worthlessness
36	Ik had vandaag last van lichamelijke klachten	I was bothered by physical symptoms today	Not at all – Very much	0 – 100	Physical discomfort
37	Ik had vandaag de neiging iets onbeheersts te doen	Today I had the tendency to do something unrestrained/wild	Not at all – Very much	0 – 100	Disorganized thoughts
38	Mijn gedachten lieten me vandaag niet los	My thoughts wouldn't leave me alone today	Not at all – Very much	0 – 100	Disorganized thoughts
39	Mijn gedachten waren vandaag versneld	My thoughts were racing today	Not at all – Very much	0 – 100	Disorganized thoughts
40	Mijn gedachten waren vandaag moeilijk te uiten	My thoughts were difficult to express today	Not at all – Very much	0 – 100	Disorganized thoughts
41	Er is vandaag iets vreemds met mij of om mij heen gebeurd dat ik moeilijk kon verklaren	Today something strange happened to me or around me that was difficult for me to explain	Not at all – Very much	1 – 7	Strange impressions / Delusions
42	Ik hoorde vandaag stemmen die anderen niet hoorden	Today I heard voices that others couldn't hear	Not at all – Very much	1 – 7	Hallucinations
43	Ik zag vandaag dingen die anderen niet zagen	Today I saw things that others couldn't see	Not at all – Very much	1 – 7	Hallucinations
44	Ik had vandaag het	Today I had the	Not at all – Very much	0 – 100	Paranoia

	gevoel dat anderen me niet mochten	feeling that others did not like me			
45	Ik had vandaag het gevoel dat anderen mijn gedachten konden lezen	I felt that others could read my thoughts today	Not at all – Very much	0 – 100	Delusions
46	Ik voelde me vandaag onwerkelijk	I felt unreal today	Not at all – Very much	0 – 100	Delusions
47	Ik had vandaag het gevoel dat anderen controle over me uitoefenden	I felt that others could control me today	Not at all – Very much	0 – 100	Delusions
48	Ik kon vandaag plezier ervaren wanneer er leuke dingen gebeurden	I could experience pleasure when nice things happened today	Not at all – Very much	0 – 100	Flat affect /anhedonia
49	Er kwam vandaag weinig uit mijn handen	I did not get many things done today	Not at all – Very much	0 – 100	Motivation / drive
50	Ik had vandaag zin om dingen te ondernemen	I felt like undertaking something to day	Not at all – Very much	0 – 100	Motivation / drive
51	Ik deed dingen ‘op de automatische piloot’, zonder mij erg bewust te zijn van wat ik aan het doen was	I did things on automatic without being conscious of what I was doing today	Not at all – Very much	0 – 100	Mindfulness
52	Mijn eetlust was vandaag	My appetite today was	Smaller than normal – Larger than normal	0 – 100	Appetite
53	Hoe gestrest was je vandaag?	How stressed were you today?	Not at all – Very much	0 – 100	Stress

54	In welke mate zijn er vandaag positieve gebeurtenissen geweest?	To what extent did positive events happen today?	Not at all – Very much	0 – 100	Positive events
Instruction	*Denk aan de belangrijkste positieve gebeurtenis van de afgelopen dag*	*Think about the most important positive event of today*			
55	Hoe plezierig was deze gebeurtenis?	How pleasant was this event?	Neutral – Very pleasant	0 – 100	Positive events
56	Hoe belangrijk was deze gebeurtenis voor mij?	How important was this positive event to me?	Very unimportant – Very important	0 – 100	Positive events
57	Was deze positieve gebeurtenis gepland?	Was this positive event planned?	• No (skip to 59) • Yes	0 - 1	Positive events
58	Ik keek er naar uit	I was looking forward to it	Not at all – Very much	0 – 100	Positive events
59	In welke mate zijn er vandaag negatieve gebeurtenissen geweest?	To what extent did negative events happen today?	Not at all – Very much	0 – 100	Negative events
Instruction	*Denk aan de belangrijkste negatieve gebeurtenis van de afgelopen dag*	*Think about the most important negative event of today*			
60	Hoe onplezierig was deze gebeurtenis?	How unpleasant was this event?	Very unpleasant - Neutral	0 – 100	Negative events
61	Hoe belangrijk was deze gebeurtenis	How important was this negative event to	Very unimportant – Very important	0 – 100	Negative events

		voor mij?	me?			
62		Was deze negatieve gebeurtenis gepland?	Was this negative event planned?	• No (skip to 59) • Yes	0 - 1	Negative events
	63	Ik zag er tegen op	I dreaded it	Not at all – Very much	0 – 100	Negative events
64		Welke gebeurtenis was het meest spannend of stressvol?	Which event was most exciting or stressful?	• The negative event • The positive event	1 - 2	Event stressfulness
65		Hoe stressvol of spannend was deze gebeurtenis?	How stressful or exciting was this event?	Not at all – Very much	0 – 100	Event stressfulness
66		Hoe ben je met deze (stressvolle) gebeurtenis omgegaan? Ik ben hiermee omgegaan door:	How did you cope with this event? I dealt with this by	• Actively addressing or solving the situation • Talking to someone • Avoiding the situation • Seeking distraction (e.g. exercise, smoking, watching television) • Thinking about it a lot • Expressing my frustration • Reassuring myself or by putting things in perspective • Gently observing and accepting my feelings • None of the above	0 – 1 for every check box	Coping
67		Hoeveel ben ik vandaag alleen geweest?	How much was I alone today?	Not for a moment – The whole day (if "Not for a moment", skip to 69) (if "The whole day", go to 68, and thereafter skip to 70)	1 - 7	Social context
	68	Ik was liever wat meer in gezelschap	I would have preferred more company	Not at all – Very much	0 – 100	Social context

		geweest			
	69	Ik vond het gezelschap van vandaag overwegend	I found today's company mostly	Very unpleasant – Very pleasant	0 – 100	Social context
70		Voelde je je vandaag gesteund?	Did you feel supported today?	Not at all – Very much	0 – 100	Social context
71		Ik had liever meer steun gevoeld	I would have liked to feel more support	Not at all – Very much	0 – 100	Social context
72		Heb je vandaag met iemand een gesprek gevoerd?	Have you had a conversation with someone today?	• No (skip to 78) • Yes	0 – 1	Social context
Instruction		*Denk aan het voor jou belangrijkste gesprek van vandaag (mag ook via telefoon of mobiele berichtenapp)*	*Think about the most important conversation of today*			

	73	Met wie was dit gesprek?	With whom was this conversation?	• Family (except partner)
				  ○ Father
				  ○ Mother
				  ○ Other
				• Partner
				• Friend
				• Other
					1 - 7	Social context

	74	Hoe kritisch was deze persoon naar jou toe?	How critical was this person towards you?	Not at all – Very much	0 – 100	Expressed emotions
	75	Hoe warm was deze persoon naar jou toe?	How warm was this person towards you?	Not at all – Very much	0 – 100	Expressed emotions
	76	In welke mate	To what extent did this	Not at all – Very much	0 – 100	Expressed

		bemoeide deze persoon zich teveel met jou?	person interfere too much with you			emotions
	77	Ik voel me verbonden met deze persoon	I felt connected with this person	Not at all – Very much	0 – 100	Social context
78		Ik heb vandaag de volgende middelen gebruikt:	I have used the following substance today	• Prescribed medication • Alcohol • Hash/Cannabis • Stimulating drugs • Calming drugs • Other drugs • None of the above		Substance use
79		Ik ben vandaag lichamelijk actief geweest	I have been physically active today	Not at all – Very much	0 – 100	Physical activity
80		Heb je vandaag goed kunnen functioneren?	Were you able to function well today?	Not at all – Very much	0 – 100	Functioning
Instruction		*Het volgende item gaat over morgen*	*The next item is about tomorrow*			
81		Ik heb zin in morgen	I look forward to tomorrow	Not at all – Very much	0 – 100	Interest / motivation

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

A study protocol for a prospective cohort study examining the predictive potential of dynamic symptom networks for the onset and progression of psychosis: The Mapping Individual Routes of Risk and Resilience (Mirorr) study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019059.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Sep-2017
Complete List of Authors:	Booij, Sanne; University of Groningen, University Medical Center Groningen, Interdisciplinary Center Psychopathology and Emotion regulation Wichers, Marieke; University of Groningen, University Medical Center Groningen, Interdisciplinary Center Psychopathology and Emotion regulation de Jonge, Peter; University of Groningen, Department of Developmental Psychology Sytema, Sjoerd; University of Groningen, University Medical Center Groningen, Interdisciplinary Center Psychopathology and Emotion regulation van Os, Jim; Maastricht University Medical Centre, Psychiatry and Medical Psychology Wunderink, Lex; Friesland Mental Health Services, Department of Research and Education Wigman, Johanna; University of Groningen, University Medical Center Groningen, Interdisciplinary Center Psychopathology and Emotion regulation
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	PSYCHIATRY, Child & adolescent psychiatry < PSYCHIATRY, Schizophrenia & psychotic disorders < PSYCHIATRY, MENTAL HEALTH

Title: A study protocol for a prospective cohort study examining the predictive potential of dynamic symptom networks for the onset and progression of psychosis: The Mapping Individual Routes of Risk and Resilience (Mirorr) study

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Abstract (295 words)

Introduction: Our current ability to predict the course and outcome of early psychotic symptoms is limited, hampering timely treatment. To improve our understanding of the development of psychosis, a different approach to psychopathology may be productive. We propose to re-conceptualize psychopathology from a network perspective, according to which symptoms act as a dynamic, interconnected system, impacting on each other over time and across diagnostic boundaries to form symptom networks. Adopting this network approach, the Mapping Individual Routes of Risk and Resilience (Mirorr) study aims to determine whether characteristics of symptom networks can predict illness course and outcome of early psychotic symptoms.

Methods and analysis: The sample consists of N=100 participants aged 18-35 years, divided into four subgroups (N=4x25) with increasing levels of severity of psychopathology, representing successive stages of clinical progression. Individuals representing the initial stage have a relatively low expression of psychotic experiences (general population), whereas individuals representing the end stage are help-seeking and display a psychometric expression of psychosis, putting them at ultra-high risk for transition to psychotic disorder. At baseline and 1-year follow-up, participants report their symptoms, affective states and experiences for three consecutive months in short, daily questionnaires on their smartphone, which will be used to map individual networks. Network parameters, including the strength and directionality of symptom connections and centrality indices, will be estimated, and associated to individual differences in and within-individual progression through stages of clinical severity and functioning over the next three years.

Ethics and dissemination: The study has been approved by the local medical ethical committee (ABR no. NL52974.042.15). The results of the study will be published in (inter)national peer-reviewed journals, presented at research, clinical and general public conferences. The results will assist in improving and fine-tuning dynamic models of psychopathology, stimulating both clinical and scientific progress.

Trial registration:

Netherlands Trial Register NTR6205, Registered 27 October 2016.

http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6205

Strengths and limitations of this study:

- One of the first studies examining the predictive potential of dynamic symptoms networks for the onset and progression of psychopathology
- The study design allows considering within- and between-individual variation in symptomatology, both at the micro (day) and macro (year) level
- A dynamic, transdiagnostic approach is adopted; outcome measures include clinical stage, diagnosis, symptoms of a broad range of disorders and functioning
- With three yearly follow-ups, we may not capture all transitions to psychosis
- The exploratory nature of the study warrants replication of the findings

Words (main text): 5035

Introduction

Psychotic disorders are among the most severe mental disorders in terms of individual and societal impact [1, 2]. Therefore, early detection and intervention in psychosis should be highly prioritized [3], which is increasingly acknowledged [4]. Psychosis is currently conceptualized as a continuum of psychotic severity, encompassing both subclinical and clinical expression [5]. As such, psychotic symptoms do not only present in the context of psychotic disorders, but also across other, non-psychotic disorders [6, 7].

Current diagnostic systems in psychiatry are challenged by issues such as high levels of comorbidity, clinical heterogeneity, non-specific treatment effects, and lack of diagnosis-specific biological/ cognitive markers [8-12]. Despite this, traditional diagnoses still dominate psychiatric research, hampering scientific progress. These diagnoses are based on clinical presentation of adults with long-established illness [13], and classify individuals according to distinct diagnostic labels [8] (e.g. schizophrenia or major depressive disorder). However, it is increasingly acknowledged that psychopathology is expressed dimensionally, representing a quantitative as well as qualitative deviations from mental health [8, 14-19]. In addition, it is increasingly accepted that mental disorders do not emerge fully formed in adulthood but evolve gradually, often manifesting for the first time already in adolescence [20, 21].

A model that was designed to capture this continuity of both severity and time is the clinical staging model [22, 23]. This model describes psychopathology as ranging, through subsequent but qualitatively different stages, from increased risk of mental illness at the lowest level through progressive stages of severity, resulting in separable but overlapping syndromes at the highest

levels [24, 25]. Stage 0 represents individuals at increased risk without symptoms; Stage 1a represents 'help-seeking' individuals with mild, non-specific symptoms; Stage 1b represents individuals with an 'attenuated syndrome', with moderate but subthreshold symptoms and moderate functional decline; Stage 2 holds individuals with a first episode of a clinical, 'discrete', disorder; Stage 3 holds individuals with persistent or recurrent illness [13, 22, 23] and Stage 4 represents individuals with chronic illness. This clinical staging model further hypothesizes that psychopathological expression is more multi-dimensional, non-specific and more susceptible to intervention in early stages and becomes more crystallized, disorder specific and treatment-resistant in later stages [25]. This model offers a theoretical representation that seems to fit better to the true nature and development of psychopathology [9-11, 26], and hence may improve diagnostic accuracy. It has been developed most extensively in the context of psychosis [23, 25, 27], but needs further empirical validation. Longitudinal studies assessing predictive validity of the model have mostly concentrated around the transition from stage 1b (ultra-high risk) to stage 2 (first psychotic episode), and found 3-year transition rates of 36% [28]. In addition, some biological and cognitive measures seem to be more abnormal in more severe stages, and these measures seem to change in patients who progress in stage [29, 30]. Finally, some treatments seem more effective for individuals in early stages [30]. Taken together, these studies provide at least some support for the clinical staging model of psychosis. However, many questions still remain, e.g. about what drives progression through subsequent stages and how the thresholds between the stages should be defined exactly.

The expression and development of early psychotic symptoms are highly variable [31-34] and difficult to predict [28, 35]. One reason for this is that many studies so far have focused on early

psychotic symptoms as specific predictors of later schizophrenia. However, this approach may be too narrow [25, 33, 36] because early psychotic symptoms are often transitory [37-39], also occur in the context of [6, 7, 40-42] and predict other mental disorders [28, 37, 43, 44], and vice versa [45-47]. High levels of comorbidity [48] and overlap of risk factors [49-52] also challenge the assumed independence of psychosis from other symptom domains. In addition, the information that is used to predict course and outcome is often based on cross-sectional assessment of symptoms and comparisons are often made at the group level. However, symptoms can vary substantially over time, both over short (i.e. days) and long intervals (months, years), within one individual, and can also cross diagnostic borders [53]. This means that the clinical picture can change, particularly in the early phase of a disorder [25]. These characteristics of psychopathology suggest that the ´static´ model prediction may not be fit for the purpose. This is reflected in the modest accuracy and replicability of static prediction models in the psychosis prediction field [54-56].

The above-mentioned challenges may be overcome by taking a different approach towards the conceptualization of psychopathology, its measurement and the way we model it. By taking a more transdiagnostic approach, incorporating symptoms and experiences from multiple (psychotic and non-psychotic) domains, the narrow focus on the sole dimension of psychosis can be broadened. Furthermore, by modelling individual patterns of symptom patterns over time, a more developmental as well as a more personalized approach can be taken that, in addition, builds on a more detailed inventory of symptomatology compared to baseline (cross-sectional) assessment scores. Finally, modelling the interconnectivity between symptoms by mapping individual symptom networks and patterns of co-occurrence in and over time could provide us

with a better idea of how psychopathology develops and may give us clues on what processes may drive progression through subsequent clinical stages [57, 58].

A network approach to psychopathology

A focus on dynamic symptom networks requires an innovative approach to psychopathology. One of the currently promising alternative approaches comes from network theory. From this network perspective, psychopathology, at a phenomenological level, is hypothesized to result from interactions between symptoms [11, 59, 60]. Mental disorders are thus represented by sets of symptoms, connected in networks by causal relations [11, 59] (see also Figure 1). These networks are dynamic and capture reciprocal influences between symptoms over time (e.g., feedback loops). Importantly, symptoms are acknowledged as causal factors in psychopathological development: one symptom (e.g., anxiety) can cause another (e.g., paranoia). This is in sharp contrast with current dominant models that represent symptoms as independent indicators of underlying, latent constructs (e.g., schizophrenia). As stress is important in the development of psychosis [61, 62], the sensitivity of symptom networks to risk-enhancing (trauma) and risk-reducing (coping, social support) factors [63, 64] also needs attention. The network approach has been successfully applied in other fields [65, 66], but is relatively novel in psychiatry, where it has been investigated mainly in common mental disorders [67], but not psychosis.

Aims and hypotheses

With the Mapping Individual Routes of Risk and Resilience (Mirorr) study, we aim to investigate the hypothesis of dynamic symptom networks as the basis of psychopathology in

general and psychosis in particular. The key hypothesis to be tested centres on the question whether individual networks of a broad scope of transdiagnostic symptoms can predict course and outcome of early psychopathology in young individuals at increased risk for psychosis and other severe mental illness. Furthermore, we aim to investigate the additional hypothesis of symptom networks as markers/indicators of progression of illness through successive clinical stages. Taking a broader, multidimensional and process-oriented approach, we will examine how symptoms of multiple domains influence each other over time and across diagnostic boundaries, in interaction with environmental factors. More specifically, we hypothesize that different clinical stages will be characterized by different symptom networks. In addition, we expect that characteristics of these networks can predict progression through clinical stages. We will explore the predictive potential of several characteristics, such as the strength and directionality of symptom connections (see Figure 1) and centrality indices (information about the position of a symptom in the network). Finally, we will evaluate the predictive potential of these characteristics against (more) static assessments of symptom severity.

The Mirorr study is unique in its design and in its attempt to (i) bring together a network approach to psychopathology and the clinical staging model, (ii) take a broader perspective on mental illness by (a) taking a transdiagnostic approach towards symptomatology and (b) defining outcome in more broadly in the context of clinical staging (incorporating both clinical and functional outcomes), and (iii) modelling individual symptom networks over time by using time-series data, enabling us to model more personalized pathways of psychopathological development.

Outcome measures

Traditionally, research in the field of psychosis focuses mostly on transition from clinical high risk to a first episode of psychosis [68]. However, there is growing awareness that this may be arbitrary, especially in the context of a staging model that acknowledges expression of illness along a much broader severity spectrum. In addition, functional outcome is becoming more and more an important outcome of interest, as it has been shown that both clinical and functional outcome are important but not always congruent [69-71]. Working from a clinical staging perspective, important outcomes to investigate include therefore progression through clinical stages, functioning and need for care.

Please insert Figure 1 here.

Methods and analysis

Study design

This study combines idiographic (within-person) and nomothetic (between-person) observational study designs. The nomothetic aspect of the study is captured by questionnaire and interview data at baseline and three yearly follow measurement waves. Among other things, symptomatology, functioning and need for care will be assessed (outcome measures), as well as risk and protective factors. The idiographic aspect is captured by diary assessments at baseline and the first follow-up wave. During the diary periods, participants will complete a diary questionnaire daily for a period of 90 days on their smartphone, regarding symptoms, emotions,

functioning and stress. These diary data are used to map individual symptom networks. For the second diary period, participants can also opt to keep continuing the questionnaire follow-ups, but not have a second diary period. A flowchart of the study is presented in Figure 2.

Please insert Figure 2 here.

Study population

The total sample comprises of 175 individuals of 18-35 years, whereof 100 will enter the main study (i.e. the daily diary study and the yearly follow-ups). For the main study, there will be four subsamples, all n=25 (Figure 3) with each subgroup having an increasingly more severe psychopathological level and thus representing subsequent clinical stages. For subsample 1 (lowest level of psychopathology and thus lowest clinical stage), 100 individuals will be randomly selected from the general population in the North of the Netherlands and administered the Community Assessment of Psychic Experiences (CAPE) [72]. Of all the respondents who meet the inclusion and exclusion criteria of the study, the highest scoring quartile will be included in the main study. For subsamples 2-4, individuals will be recruited from mental health care institutions in the four Northern provinces in The Netherlands. For all individuals who are referred to mental health care, psychotic symptoms are routinely screened by means of, among other things, the Prodromal Questionnaire (PQ) [73]. If the score on the PQ is 6 or higher, the Comprehensive Assessment of At Risk Mental State (CAARMS) [74] is administered as well. With these scores it is determined for which subsample (2-4, explained below) eligible subjects will be recruited, where a higher subsample indicates higher levels of psychopathology.

Please insert Figure 3 here.

In order to be eligible to participate in the study, subjects must meet all of the following criteria: 1) age between 18 and 35 years, 2) read and speak Dutch fluently, 3) capable of following the research procedures, 4) provide Informed Consent. In addition, participants of subsample 1 should *not* be in clinical care for mental health at the moment of screening. In contrast, participants of subsample 2-4 *should* currently be in clinical care for mental health. In addition, participants of subsample 2 should have mild, non-psychotic psychopathology, as evidenced by a score below 6 on the PQ, participants of subsample 3 should have mild psychopathology including subclinical psychotic symptoms, as evidenced by a score of or above 6 on the PQ, but are not at ultra-high risk (UHR) for psychosis, as indexed by the CAARMS. Finally, participants of subsample 4 should be at UHR for psychosis, as indexed by the CAARMS. Exclusions criteria are: 1) a history of or current psychotic episode, according to the Diagnostic and Statistical manual of Mental Disorders-IV (DSM-IV) criteria; 2) significant hearing or visual problems impairments; 3) pregnancy, as stated on a general health questionnaire.

Procedure

Recruitment

To recruit subsample 1, the study will be announced at several university sites, public places in Groningen, and social media (start recruitment: September 2015). Interested individuals can contact the researchers by phone or e-mail for more information. They will then be sent an information letter, flyer, informed consent form and the initial screenings questionnaires. After receiving the completed screening questionnaires and informed consent forms, the 25 (out of

100) individuals with the highest CAPE scores will be invited to participate in the main study (first inclusion: December 2015). For subsample 2-4, individuals will be recruited from mental health care institutions in four northern Dutch provinces (first inclusion: April 2016). To which subsample they will be recruited is determined using the instruments described under study population. For these sites where patients give their consent for receiving information about ongoing research projects, a package containing detailed information on the study (information letter and flyer), along with screening questionnaires and an informed consent form will be sent to potential participants. Interested individuals can fill out and return requested forms (including informed consent form). After receiving the requested forms, an individual's therapist will be consulted about several exclusion criteria. For these sites where participants do not give consent in advance, the individual's clinical worker will be provided a package containing detailed information on the study (information letter and flyer), along with screening questionnaires and an informed consent form. The clinical worker will pre-screen his/her client on the exclusion criteria of the study and hand over the package if he/she fits the profile of the study. Study participants can continue their therapy and medical treatment as usual; they will be asked to register any changes in medication or treatment during the daily ambulatory assessments.

Screening

The information package that interested individuals receive contains an information letter, two screening questionnaires and an informed consent form. All potential participants can ask questions before completing informed consent form or the screening questionnaires. As mentioned in the information letter, in case subjects should decide to participate, they should fill out and send back these questionnaires and the informed consent form. This consent form covers

the baseline ambulatory assessment period and the yearly follow-up assessments (three in total). On this consent form permission will be asked to re-invite subjects for the follow-up ambulatory assessment period, for which they have to complete a separate consent form (one year later). Also, permission will be asked to use data from the psychiatric case register of the North of the Netherlands. The first screening questionnaire is a screening questionnaire on general health, containing questions on demographics, health complaints (such as visual or hearing impairments), pregnancy, drug and alcohol use, medication use, and mental health problems. This will be used to screen on exclusion criteria. The second screening questionnaire is the CAPE. This instrument is used to screen individuals recruited from the general population (subsample 1) on psychotic experiences but will be administered to all participants to enable group comparisons on the level of subclinical psychotic experiences. The highest scoring quartile (n=25) will subsequently be included in the main study. Subjects will have one week to decide about participation.

Baseline interview and ambulatory assessments (year one)

If subjects are eligible to enter the study and agree to participate, they will be invited (by telephone or e-mail) for an introduction interview at the University Medical Centre Groningen. A few days before the interview, self-report questionnaires will be administered via email (see data management for more information). The questionnaires assess symptomatology, functioning, clinical stage, and factors of risk and resilience. During the interview, the study will be explained to them in detail and a diagnostic psychiatric interview will be held. If in an exceptional case the participant does not possess a smartphone, this will be provided to the participant during the study period. An appointment for an end-of-study interview will be planned. Also, the

participants will be asked to designate suitable moments at which the researcher can call him/her to inquire on the progression of the study and to help with any problems the participant may experience.

The participants then start completing the electronic daily diary for three months. Every evening, they receive a text message with a link which directs them to a web-based diary questionnaire in a secure environment. Measurements are always in the evening, asking about the past day; exact times can vary per person (but not per day) and are fixed according to the participant's wishes. However, *all* participants have 24 hours between each measurement point. For example, participant A will always receive her text message at 22.00 and participant B always at 21.15. A window of one and a half hour will be allowed to fill in the diary, and reminder messages will be send every half hour. Short questions will be presented on sequential screens, which are mainly answered using visual analogue scales. During the research period, participants are also provided a paper log, in which they can note any unusual events, start of or changes in medication use and problems they encounter with the research procedures. The researchers will telephone the participants six times during the study period (every other week), to motivate the participant, answer questions about the study procedures and provide technical help. They will also be available by telephone and e-mail if participants need help at other moments.

During the end-of-ambulatory-assessment (3 months after baseline) interview participants will fill out an online questionnaire battery once more, and report on any changes in medical treatment. Furthermore, they will also be asked to comment on the data collection and the study in general. We will use this information to check whether the study affected their thoughts and

behaviours in any way, whether there had been special events that might have affected the data collected.

Follow-up assessments

One, two and three years after baseline, all participants will receive questionnaires about functioning and clinical stage via email. The participants will be able to fill these in at home. Shortly after filling in the questionnaires, participants will be interviewed by telephone or face-to-face at one of our research facilities, depending on their preferences, to establish the presence/absence of psychiatric disorders with a diagnostic interview. In addition, to distinguish individuals in clinical stage 1a from individuals in clinical stage 1b (all individuals with a score of 6 or higher on the PQ-16), data from the CAARMS interview is needed. Participants will be reminded about the follow-up assessments a few weeks before the actual follow-up by means of an information letter.

Follow-up ambulatory assessment period (year two)

In the aforementioned information letter, participants will also read information about a second ambulatory assessment period that they can enrol in. If they are interested, they are invited for another introduction interview (given that they still fulfil the in- and exclusion criteria as evidenced by their answers to an online version of a general health questionnaire). This interview is similar to the introduction interview at baseline (i.e., questionnaire battery and procedures). An exception is that questionnaires about symptomatology, functioning and clinical stage will not be administered, because they have been covered already by the usual follow-up assessments. Participants then start their second three-month period of ambulatory assessments one year after

the first diary period. The end-of-ambulatory-assessment interview will take place, again with similar questionnaires to the one held at baseline.

Instruments

A complete overview of the instruments used throughout the study is presented in Table 1.

Please insert Table 1 here.

Diary measures

The items assessed in the daily questionnaires will be used to model individual networks of symptoms, experiences and emotions. Items included in the dairy questionnaires were chosen from a transdiagnostic perspective and cover a broad range of feelings and experiences that are characteristic for (subclinical) psychotic experiences, depression, anxiety, mania, obsessive compulsive behaviour and anger. These disorders are known for the co-occurrence of psychotic symptoms [6, 7] and comorbidity [48]. For the complete item list, see Additional file 1, Table S1.

Positive psychotic experiences can be divided into five categories, namely paranoia, delusions, hallucinations, megalomania, and paranormal beliefs [75]. Because paranormal beliefs are often stable over time, we will include items covering the first four categories. Negative symptoms of psychosis will be covered by items about flattened affect (e.g., anhedonia, low motivation, social withdrawal), which resemble closely the negative symptoms of the CAPE. Most items are adopted from previous ESM studies [76-78], and all items are adapted for daily use.

Symptoms of depression will be measured using items that correspond closely to the patient health questionnaire (PHQ-9) [79], a self-administered questionnaire for screening and measuring the severity of depression. Anxiety symptoms will be measured using items that correspond closely to the Hospital Anxiety and Depression Scales – Anxiety (HADS-A) [80]. Mania, obsessive compulsive behaviour and anger are measured with items that correspond closely to items from the DSM-V – screener for the corresponding clinical disorders [81].

Positive and negative mood states over the past day will be measured with 12 items from the circumplex model of affect [82, 83]. Momentary affect will be measured with an item for valence ("I feel unpleasant – pleasant") and activation ("I feel aroused/activated – quiet/still") at the beginning of each diary entry. Other items cover sleep, daily activities and situations that may influence psychiatric symptoms, such as positive and negative events, social interactions, coping behaviour, physical activity and drug use.

Follow-up measures

Important outcomes that are linked to the above described network characteristics are (progression through) clinical stages, functioning and need for care. Progression through clinical stages will be assessed with the PQ-16, the CAPE and the CAARMS, the Symptom Check List (SCL-90) [84] and the Schedules for Clinical Assessment in Neuropsychiatry, short version (mini-SCAN) [85]. Social functioning will be assessed using the Groningse Vragenlijst voor Sociaal Gedrag (GVSG-45) [86] and the Flourishing Scale [87]. Need for care will be assessed using self-reported information on care use. Additionally, need for care will be assessed by

linking data from the psychiatric case registry to our sample when approved by the participant (as stated on the informed consent form). Specifically, the frequency and type of care use throughout the study period will be obtained.

Assessments pre- and post-daily diary period(s)

Before and after the daily diary assessments, several questionnaires will be administered to assess symptomatology, functioning and several risk and resilience factors. Psychotic symptoms will be assessed with the CAPE; depression and anxiety symptoms with the Depression Anxiety and Stress Scale (DASS) [88]; mania symptoms with the Altman Self-Rating Mania Scale (ASRM-NL) [89], social support with the Social Support List (SLL) [90]; resilience with the Brief Resilience Scale (BRS) [91] and coping style with the Utrechtse Coping Lijst (UCL) [92]. Furthermore, physical activity levels will be tracked with an accelerometer, the ActiCal® (Respironics, Bend, OR, USA), during the first two weeks of the second diary period. Output of this instrument will be presented as Energy Expenditure and Metabolic Equivalent of Task. The physical activity measurements are added to serve as a pilot study, and are not obligatory.

At baseline, sleep habits will be assessed with the Munich Chronotype Questionnaire (MCTQ) [93] to optimize the diary assessment process. Also, potential confounders such as smoking, alcohol/drug consumption, socio-economic status, Body Mass Index will be registered by means of a general health questionnaire. In addition, stressful life events will be assessed, using the list of threatening experiences [94]. Finally, pertaining to subgroup 4 only, social cognition will be assessed using the Faux Pas Task [95] and bonding with parents will be assessed with the

Inventory of Parent and Peer Attachment (IPPA) [96, 97]. These factors may be of importance in determining a transition from an UHR status to psychosis.

Data analysis plan

To map individual symptom networks of day-to-day symptom levels, multivariate time-series analysis will be employed on each individual's time series data. Specifically, vector autoregression (VAR) models will be applied [98]. These models are particularly suited for investigating the temporal dynamics between two or more variables. The resulting associations between symptoms will subsequently be presented as networks, and network parameters will be estimated. These include (but are not limited to) the strength and directionality of symptom connections (see Figure 1) and centrality indices (information about the position of a symptom in the network). Next, symptom networks will be compared (i) across different subgroups of severity and (ii) when the second diary period is completed, within each individual.

In addition, a data-driven approach will be used to identify individuals with similar symptom network characteristics by (1) qualitative network comparison, (2) quantitative comparison of centrality indices [99, 100], and (3) longitudinal mixture models [101]. These subgroups will then be compared on their levels of symptomatology and functioning and on course of symptomatology over time. Furthermore, the predictive value of the network parameters will be compared to the predictive value of usual predictors of illness course, namely cross-sectionally assessed level of (subclinical) psychotic pathology. Specifically, sensitivity and specificity of these network characteristics can be compared to sensitivity and specificity of baseline

subclinical levels of psychotic symptoms (CAPE) and general psychopathology (SCL-90). Finally, risk and resilience factors, such as stressful events, social interactions, physical activity, coping and resilience, may also influence symptoms and, importantly, their dynamics in the network, but may do so differently in individuals with good or poor clinical and functional outcome. The role of these factors will be addressed by including them in individual network analyses to examine their direct and indirect impact on symptomatology and each other.
To control for potential confounding effects of demographic factors, such as sex, age and social economic status, these variables will be added as covariates to all group level analyses.

Based on previous work [102, 103], we expect no more than 10% missing data. Missing values will be imputed with expectation-maximization imputation, following special recommendations for time-series datasets [104]. A (two-sided) p-value of 0.05 is applied for statistical testing.

Sample size and power

Within-person analyses: constructing individual symptom networks

Exact sample size calculations are not possible in studies using VAR, as it is typically unclear in such studies what effect size can be expected. This is because the direction of causality and the number of lagged influences in the system under investigation are usually unknown and bidirectional and feedback effects can be present as well [98]. However, as previous work from our group [102, 105, 106] and work of others [107] suggests, 60-90 measurements suffice to reliably identify reciprocal associations between multiple variables.

Between-person analyses: associating symptom networks to clinical stage

In the between-person analyses, the data have a multilevel structure. Therefore, the unilevel equivalent of the multilevel sample size [108] was taken to calculate the power, assuming a conservative intraclass-correlation of 0.8. Assuming differences of 0.05 in mean coefficients (s.d. = 0.07) between the different groups [109], the proposed study has a power of 0.8 (to detect significant differences at $p<0.05$). Subgroups of N=25 are large enough to take into account effects of several covariates [110].

Ethics and dissemination

This study has been approved by the medical ethical committee of the University Medical Centre Groningen (UMCG), Groningen, The Netherlands (registration number MEC no. 2015/159, ABR no. NL52974.042.15). The study will be conducted in accordance with the Helsinki Declaration, meaning that participation is voluntary and written informed consent will be obtained. Several protocols have been developed for situations where clinical care may be warranted, e.g. in case of disclosure of suicidal thoughts, or in case of UHR status in one of the lower risk groups.

An online outcome monitoring system, called RoQua (www.roqua.nl) is used for data collection and data storage, to which only designated researchers have access via the use of passwords combined with google authentication. Participants have access to the questionnaires via a link in their e-mail inbox. The safety of this system is guaranteed by the UMCG (an 'In Control Statement' is available on request). Data management is also organized according to UMCG standards, including a strict separation of identifying patient data (name, date of birth etc.) and the anonymous datasets available for the researchers.

Data gathering was not completed when this manuscript was submitted. After the study has ended and the study's main results have been published, the data obtained by this study will become available on reasonable request. Requests should be sent to j.t.w.wigman@umcg.nl with the topic name MIRORR data. The results of the study will be published in (inter)national peer-reviewed journals, presented at research, clinical and general public conferences.

Discussion

Current diagnostic systems are increasingly criticized by mental health professionals, researchers and users of mental health care [9, 12, 26, 111]. Conceptualization of psychopathology in terms of (i) clinical staging (at macro level) and (ii) dynamic, individual symptom networks (at a more micro level), which is the purpose of this study, represents a promising avenue to tackle both scientific and clinical problems. From a scientific perspective, improving our understanding of the factors driving the development of psychopathology by investigating how symptoms influence each other will enhance our ability to identify valid phenotypes to predict onset of (psychotic) mental disorders and to link with other relevant information (e.g., genetic or endophenotypic variation). From a clinical perspective, a better understanding of why psychotic symptoms can lead to a need for care in some, but resolve spontaneously in others, will help mental health professionals to adequately recognize the early needs of individuals who are likely to develop mental illness or functional impairments. This is important because interventions are both more effective and less invasive when applied early in the course of illness [112]. In more progressive clinical stages, deeper knowledge of the dynamic ways symptoms impact on each other will help to differentiate between those likely to recover or to deteriorate and between

those likely to be responsive or resistant to treatment. Using symptom networks will improve the application of individually tailored, person-based interventions, adapted to one's current clinical stage and symptomatology, as different stages require different types of intervention. Since personalised interventions better fit individual needs, they will result in enhanced treatment response [113], reducing the costs of mental disorders at both personal and societal level. Thus, the use of symptom networks will assist in improving and fine-tuning dynamic models of psychopathology, which will stimulate both clinical (in terms of both diagnostics and intervention) and scientific progress.

Acknowledgements

We would like to thank the ROQUA team for their collaboration and for building and maintaining the smartphone web-based (diary) questionnaires. We are grateful to Laura Steenhuis, Roos Willemsen, Marike Fowler, Cornelie Glasbergen, Marijke Muller, Eliese van Deelen, Marion van Dijk, Sieberen Veenstra, Marietta Khachaturyan and Thirza Osinga for their contributions to the field work and data management. We thank Ernst Wit and Elske Bos for their conceptual and methodological input. Finally, we thank Rob Wanders and Ando Emerencia for their help with automating the personalized feedback procedure.

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Authors' contributions

JTWW conceived the study. JTWW and SHB designed and are executing the study and drafted the first versions of the manuscript. LW, PdJ, JvO, MCW helped conceptualize the study and provided general advice and input, SS contributed to the study design, specifically to the data gathering and data management part. All authors critically reviewed the manuscript, and collaborated in the discussion of the intellectual content of the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the Netherlands Organization for Scientific Research (NWO) (Veni Dr. J.T.W. Wigman: no. 016.156.019). In addition, M. Wichers was supported by an H2020 European Research Council Consolidator Grant (ERC-CoG-2015, project 681466 – TRANS-ID). The funders had no role in the study design, data collection and analysis, decision to publish, or the preparation of the manuscript.

Competing interests

The authors declare that they have no competing interests.

814 **Tables**

Table 1. Overview of instruments.

Domain	Instrument	Method	Purpose	Time (min)	Screening	Diary pre (baseline)	Diary post	Follow-up 1	Diary pre	Diary post	Follow-up 2	Follow-up 3
					T0	T0	T0 (3m)	T1	T1	T1 (3m)	T2	T3
Demographics	Gen. Health	SR	Demogr, conf.	5	X				X‡			
	Vignette	INT	History psychosis	5	X**							
Psychosis	CAPE	SR	Psychotic Sx	6	X		X	X		X	X	X
	PQ	SR	Clinical stage	3		X†		X†			X†	X†
	CAARMS	INT	Clinical stage	30-90		X*†		X*†			X*†	X*†
Psychopathology	Mini-SCAN	INT	Diagnosis	30		X		X			X	X
	SCL-90	SR	Severity	20		X		X			X	X
	PsychCaseReg	REG	Care use	-		X		X			X	X
	Care use - extra	SR	Care use	1		X		X			X	X
	DASS	SR	Depress Anxiety Sx	3		X	X		X	X		
	ASRM	SR	Mania Sx	3		X	X		X	X		

Table 1. Continued.

Domain	Instrument	Method	Purpose	Time (min)	Scree-ning	Diary pre (baseline)	Diary post	Follow-up 1	Diary pre	Diary post	Follow-up 2	Follow-up 3
Social functio-ning	GVSG-45	SR	Social functioning	8		X		X			X	X
	Flourishing Sc	SR	Well-being	1		X		X			X	X
Risk & resil-ience	SSL	SR	Social support	7		X	X		X	X		
	IPPA	SR	Bonding	9		X#						
	BRS	SR	Resilience	2		X	X		X	X		
	UCL	SR	Coping	5		X	X		X	X		
	Brugha LTE	SR	Life events, trauma	4		X			X			
	MCTQ	SR	Sleep	3		X			X			
	Faux-Pas Task	INT	Social Cognition	5		X#						
	Actical®	SENS	Physical activity	-					X***			

Note. SR = Self-report, INT = Interview, REG = register, SENS = sensor Sx = symptoms, demogr = demographics, conf = confounders, depress = depression, T = measurement wave, m = months.

* Only administered when PQ score is 6 or higher.

** Only administered when there is a history of a psychiatric disorder according to the information on the General Health Questionnaire

*** Offered to participants as optional.

† Available as ROM data for all individuals in clinical care for mental health at each measurement wave.

‡ Send out several weeks before the daily diary period to screen on exclusion criteria

Administered only to subgroup 4

Figure titles and legends

Figure 1. Parameters of a theoretical symptom network.

Note. This figure is for illustrative purposes, and is not based on real data.

Figure 2. Flowchart.

Note. Light grey area within blue dashed square indicates optional measurements.

Figure 3. Definition of subgroups.

Additional files

Additional file 1.docx

Title: Table S1. Diary items

Description: Original Dutch diary items and their translation to English

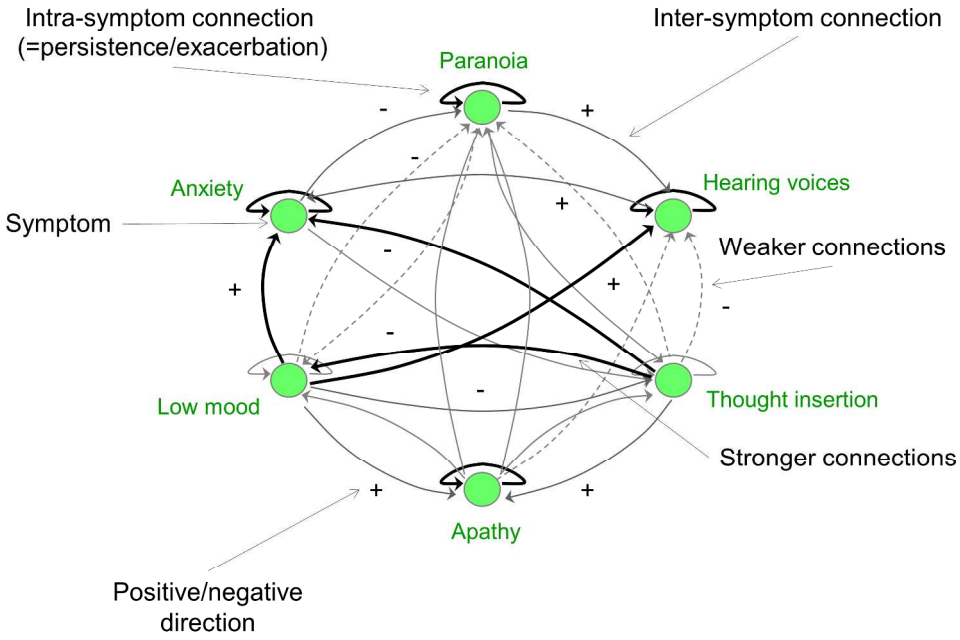

Figure 1. Parameters of a theoretical symptom network. Note. This figure is for illustrative purposes, and is not based on real data.

254x190mm (300 x 300 DPI)

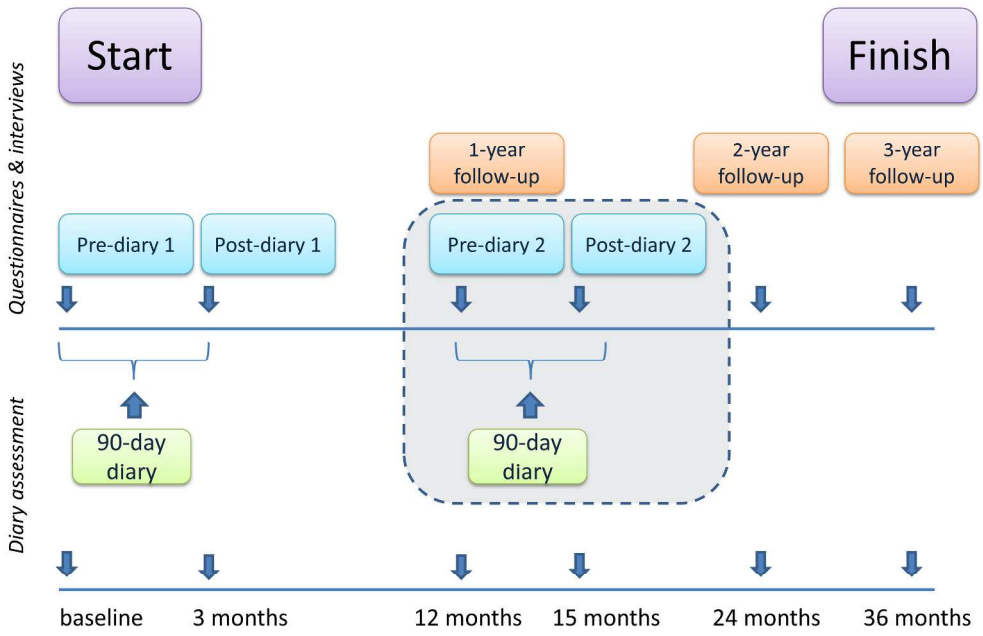

Figure 2. Flowchart. Note. Light grey area within blue dashed square indicates optional measurements.

254x190mm (300 x 300 DPI)

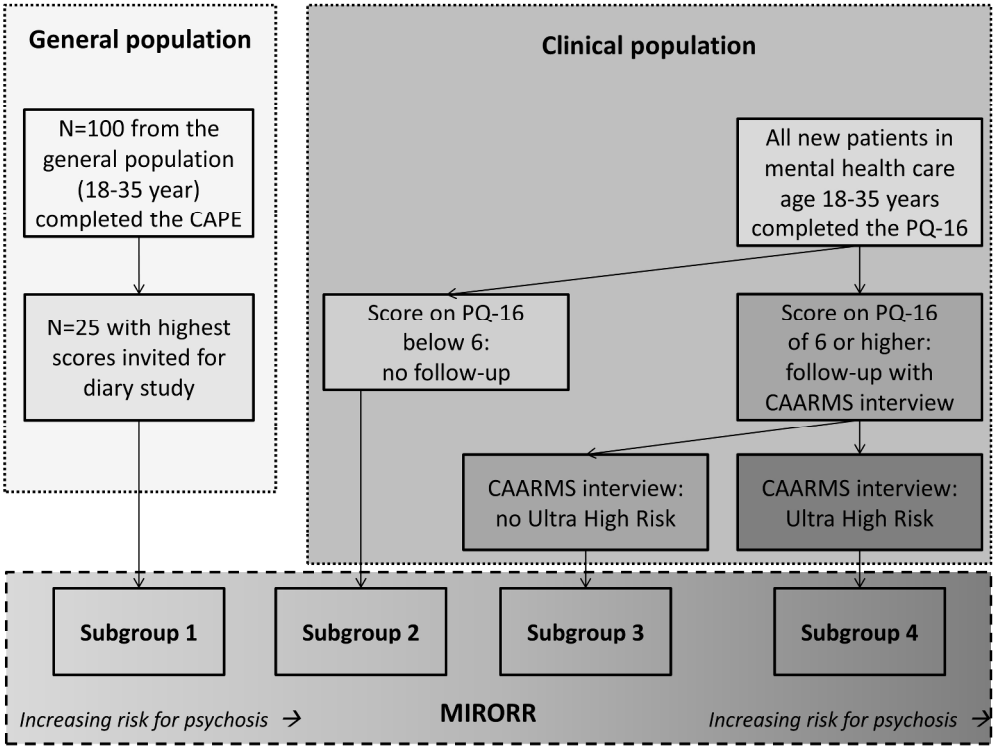

Figure 3. Definition of subgroups.

254x190mm (300 x 300 DPI)

Supplementary Table S1. Diary items.

Question	Dutch	Translation	Response range	Range	Description
1	Ik voel me nu	Right now, I feel	Very unpleasant – Very pleasant	0 - 100	Momentary affect
2	Ik voel me nu	Right now, I feel	Very restless / excited – Very quit/calm	0 - 100	Momentary affect
3	Op mijn beste moment van vandaag voelde ik mij	During my best moment of the day, I felt	Very unpleasant – Very pleasant	0 - 100	Momentary affect
4	Op mijn beste moment van vandaag voelde ik mij	During my best moment of the day, I felt	Very restless / excited – Very quit/calm	0 -100	Momentary affect
5	Wanneer was dit beste moment ongeveer? Ergens in de	Around when was this best moment? Somewhere in the	• Morning • Afternoon • Evening	1, 2, 3	Momentary affect
6	Op mijn slechtste moment van vandaag voelde ik mij	During my worst moment of the day, I felt	Very unpleasant – Very pleasant	0 - 100	Momentary affect
7	Op mijn slechtste moment van vandaag voelde ik mij	During my worst moment of the day, I felt	Very restless/ excited – Very quit/calm	0 -100	Momentary affect
8	Wanneer was dit slechtste moment ongeveer? Ergens in de	Around when was this worst moment? Somewhere in the	• Morning • Afternoon • Evening	1, 2, 3	Momentary affect
9	Heb je afgelopen nacht goed	Did you sleep well tonight?	Not at all – Very well	0 - 100	Sleep

	geslapen?				
10	Hoeveel uur heb je afgelopen nacht ongeveer geslapen?	About how many hours did you sleep tonight?	Hours, minutes	0 - 24	Sleep
11	Heb je vandaag overdag geslapen? (dutjes)	Did you sleep during the day today (naps)?	• No (skip to 13) • Yes	0 – 1	Sleep
12	Hoe lang in totaal?	How long in total did you sleep during the day today?	Hours, minutes	0 – 12	Sleep
Instruction	*Alle items gaan vanaf nu over de afgelopen dag (denk aan hoe je je vandaag gemiddeld voelde)*	*From now on, all items involve the past day (think about how you felt on average today)*			
13	Ik voelde me vandaag ontspannen	I felt relaxed today	Not at all – Very much	0 – 100	Positive deactivation
14	Ik voelde me vandaag kalm	I felt calm today	Not at all – Very much	0 – 100	Positive deactivation
15	Ik voelde me vandaag tevreden	I felt satisfied today	Not at all – Very much	0 – 100	Positive deactivation
16	Ik voelde me vandaag energiek	I felt energetic today	Not at all – Very much	0 – 100	Positive activation
17	Ik voelde me vandaag enthousiast	I felt enthusiastic today	Not at all – Very much	0 – 100	Positive activation
18	Ik voelde me vandaag opgewekt	I felt cheerful today	Not at all – Very much	0 – 100	Positive activation
19	Ik voelde me vandaag lusteloos	I felt apathetic today	Not at all – Very much	0 – 100	Negative deactivation
20	Ik voelde me vandaag moe	I felt tired today	Not at all – Very much	0 – 100	Negative deactivation
21	Ik voelde me	I felt down today	Not at all – Very much	0 – 100	Negative

	vandaag somber				deactivation
22	Ik voelde me vandaag angstig	I felt anxious today	Not at all – Very much	0 – 100	Negative activation
23	Ik voelde me vandaag onrustig	I felt restless today	Not at all – Very much	0 – 100	Negative activation
24	Ik voelde me vandaag prikkelbaar	I felt irritable today	Not at all – Very much	0 – 100	Negative activation
25	Ik voelde me vandaag geïrriteerd	I felt irritated today	Not at all – Very much	0 – 100	Irritation
26	Ik voelde me vandaag spraakzaam	I felt talkative today	Not at all – Very much	0 – 100	Spontaneity
27	Ik voelde me vandaag zelfverzekerd	I felt confident today	Not at all – Very much	0 – 100	Self confidence
28	Ik voelde me vandaag leeg/vlak	I felt empty today	Not at all – Very much	0 – 100	Flat affect / Anhedonia
29	Ik voelde me vandaag ongerust	I felt worried today	Not at all – Very much	0 – 100	Worrying
30	Ik voelde me vandaag erg speciaal	I felt very special today	Not at all – Very much	0 – 100	Delusions
31	Ik voelde me vandaag wantrouwig	I felt suspicious today	Not at all – Very much	0 – 100	Delusions
32	Ik had vandaag het gevoel te kort te schieten	Today I had the feeling of falling short	Not at all – Very much	0 – 100	Worthlessness
33	Ik kon vandaag aan wat op mijn pad kwam	Today I could handle what came my way	Not at all – Very much	0 – 100	Resilience
34	Ik kon me vandaag goed concentreren	I could concentrate well today	Not at all – Very much	0 – 100	Concentration

35	Ik vond mijn leven vandaag de moeite waard	I found my life was worthwhile today	Not at all – Very much	0 – 100	Worthlessness
36	Ik had vandaag last van lichamelijke klachten	I was bothered by physical symptoms today	Not at all – Very much	0 – 100	Physical discomfort
37	Ik had vandaag de neiging iets onbeheersts te doen	Today I had the tendency to do something unrestrained/wild	Not at all – Very much	0 – 100	Disorganized thoughts
38	Mijn gedachten lieten me vandaag niet los	My thoughts wouldn't leave me alone today	Not at all – Very much	0 – 100	Disorganized thoughts
39	Mijn gedachten waren vandaag versneld	My thoughts were racing today	Not at all – Very much	0 – 100	Disorganized thoughts
40	Mijn gedachten waren vandaag moeilijk te uiten	My thoughts were difficult to express today	Not at all – Very much	0 – 100	Disorganized thoughts
41	Er is vandaag iets vreemds met mij of om mij heen gebeurd dat ik moeilijk kon verklaren	Today something strange happened to me or around me that was difficult for me to explain	Not at all – Very much	1 – 7	Strange impressions / Delusions
42	Ik hoorde vandaag stemmen die anderen niet hoorden	Today I heard voices that others couldn't hear	Not at all – Very much	1 – 7	Hallucinations
43	Ik zag vandaag dingen die anderen niet zagen	Today I saw things that others couldn't see	Not at all – Very much	1 – 7	Hallucinations
44	Ik had vandaag het	Today I had the	Not at all – Very much	0 – 100	Paranoia

	gevoel dat anderen me niet mochten	feeling that others did not like me			
45	Ik had vandaag het gevoel dat anderen mijn gedachten konden lezen	I felt that others could read my thoughts today	Not at all – Very much	0 – 100	Delusions
46	Ik voelde me vandaag onwerkelijk	I felt unreal today	Not at all – Very much	0 – 100	Delusions
47	Ik had vandaag het gevoel dat anderen controle over me uitoefenden	I felt that others could control me today	Not at all – Very much	0 – 100	Delusions
48	Ik kon vandaag plezier ervaren wanneer er leuke dingen gebeurden	I could experience pleasure when nice things happened today	Not at all – Very much	0 – 100	Flat affect /anhedonia
49	Er kwam vandaag weinig uit mijn handen	I did not get many things done today	Not at all – Very much	0 – 100	Motivation / drive
50	Ik had vandaag zin om dingen te ondernemen	I felt like undertaking something to day	Not at all – Very much	0 – 100	Motivation / drive
51	Ik deed dingen ‘op de automatische piloot’, zonder mij erg bewust te zijn van wat ik aan het doen was	I did things on automatic without being conscious of what I was doing today	Not at all – Very much	0 – 100	Mindfulness
52	Mijn eetlust was vandaag	My appetite today was	Smaller than normal – Larger than normal	0 – 100	Appetite
53	Hoe gestrest was je vandaag?	How stressed were you today?	Not at all – Very much	0 – 100	Stress

54	In welke mate zijn er vandaag positieve gebeurtenissen geweest?	To what extent did positive events happen today?	Not at all – Very much	0 – 100	Positive events
Instruction	*Denk aan de belangrijkste positieve gebeurtenis van de afgelopen dag*	*Think about the most important positive event of today*			
55	Hoe plezierig was deze gebeurtenis?	How pleasant was this event?	Neutral – Very pleasant	0 – 100	Positive events
56	Hoe belangrijk was deze gebeurtenis voor mij?	How important was this positive event to me?	Very unimportant – Very important	0 – 100	Positive events
57	Was deze positieve gebeurtenis gepland?	Was this positive event planned?	• No (skip to 59) • Yes	0 - 1	Positive events
58	Ik keek er naar uit	I was looking forward to it	Not at all – Very much	0 – 100	Positive events
59	In welke mate zijn er vandaag negatieve gebeurtenissen geweest?	To what extent did negative events happen today?	Not at all – Very much	0 – 100	Negative events
Instruction	*Denk aan de belangrijkste negatieve gebeurtenis van de afgelopen dag*	*Think about the most important negative event of today*			
60	Hoe onplezierig was deze gebeurtenis?	How unpleasant was this event?	Very unpleasant - Neutral	0 – 100	Negative events
61	Hoe belangrijk was deze gebeurtenis	How important was this negative event to	Very unimportant – Very important	0 – 100	Negative events

		voor mij?	me?			
62		Was deze negatieve gebeurtenis gepland?	Was this negative event planned?	• No (skip to 59) • Yes	0 - 1	Negative events
	63	Ik zag er tegen op	I dreaded it	Not at all – Very much	0 – 100	Negative events
64		Welke gebeurtenis was het meest spannend of stressvol?	Which event was most exciting or stressful?	• The negative event • The positive event	1 - 2	Event stressfulness
65		Hoe stressvol of spannend was deze gebeurtenis?	How stressful or exciting was this event?	Not at all – Very much	0 – 100	Event stressfulness
66		Hoe ben je met deze (stressvolle) gebeurtenis omgegaan? Ik ben hiermee omgegaan door:	How did you cope with this event? I dealt with this by	• Actively addressing or solving the situation • Talking to someone • Avoiding the situation • Seeking distraction (e.g. exercise, smoking, watching television) • Thinking about it a lot • Expressing my frustration • Reassuring myself or by putting things in perspective • Gently observing and accepting my feelings • None of the above	0 – 1 for every check box	Coping
67		Hoeveel ben ik vandaag alleen geweest?	How much was I alone today?	Not for a moment – The whole day (if “Not for a moment”, skip to 69) (if “The whole day”, go to 68, and thereafter skip to 70)	1 - 7	Social context
	68	Ik was liever wat meer in gezelschap	I would have preferred more company	Not at all – Very much	0 – 100	Social context

		geweest				
	69	Ik vond het gezelschap van vandaag overwegend	I found today's company mostly	Very unpleasant – Very pleasant	0 – 100	Social context
70		Voelde je je vandaag gesteund?	Did you feel supported today?	Not at all – Very much	0 – 100	Social context
71		Ik had liever meer steun gevoeld	I would have liked to feel more support	Not at all – Very much	0 – 100	Social context
72		Heb je vandaag met iemand een gesprek gevoerd?	Have you had a conversation with someone today?	• No (skip to 78) • Yes	0 – 1	Social context
Instruction		*Denk aan het voor jou belangrijkste gesprek van vandaag (mag ook via telefoon of mobiele berichtenapp)*	*Think about the most important conversation of today*			
	73	Met wie was dit gesprek?	With whom was this conversation?	• Family (except partner) o Father o Mother o Other • Partner • Friend • Other	1 - 7	Social context
	74	Hoe kritisch was deze persoon naar jou toe?	How critical was this person towards you?	Not at all – Very much	0 – 100	Expressed emotions
	75	Hoe warm was deze persoon naar jou toe?	How warm was this person towards you?	Not at all – Very much	0 – 100	Expressed emotions
	76	In welke mate	To what extent did this	Not at all – Very much	0 – 100	Expressed

		bemoeide deze persoon zich teveel met jou?	person interfere too much with you			emotions
	77	Ik voel me verbonden met deze persoon	I felt connected with this person	Not at all – Very much	0 – 100	Social context
78		Ik heb vandaag de volgende middelen gebruikt:	I have used the following substance today	• Prescribed medication • Alcohol • Hash/Cannabis • Stimulating drugs • Calming drugs • Other drugs • None of the above		Substance use
79		Ik ben vandaag lichamelijk actief geweest	I have been physically active today	Not at all – Very much	0 – 100	Physical activity
80		Heb je vandaag goed kunnen functioneren?	Were you able to function well today?	Not at all – Very much	0 – 100	Functioning
Instruction		*Het volgende item gaat over morgen*	*The next item is about tomorrow*			
81		Ik heb zin in morgen	I look forward to tomorrow	Not at all – Very much	0 – 100	Interest / motivation

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.