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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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Manuscripts

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3 1 **Title: A study protocol for a prospective cohort study examining the predictive potential of**
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6 2 **dynamic symptom networks for the onset and progression of psychosis: The Mapping**
7
8 3 **Individual Routes of Risk and Resilience (Mirorr) study**

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3 35 **Abstract** (295 words)
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8 37 Introduction: Our current ability to predict the course and outcome of early psychotic symptoms
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10 38 is limited, hampering timely treatment. To improve our understanding of the development of
11
12 39 psychosis, a different approach to psychopathology may be productive. We propose to re-
13
14 40 conceptualize psychopathology from a network perspective, according to which symptoms act as
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16 41 a dynamic, interconnected system, impacting on each other over time and across diagnostic
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18 42 boundaries to form symptom networks. Adopting this network approach, the Mapping Individual
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20 43 Routes of Risk and Resilience (Mirorr) study aims to determine whether characteristics of
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22 44 symptom networks can predict illness course and outcome of early psychotic symptoms.
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29 46 Methods and analysis: The sample consists of N=100 participants aged 18-35 years, divided into
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31 47 four subgroups (N=4x25) with increasing levels of severity of psychopathology, representing
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33 48 successive stages of clinical progression. Individuals representing the initial stage have a
34
35 49 relatively low expression of psychotic experiences (general population), whereas individuals
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37 50 representing the end stage are help-seeking and display a psychometric expression of psychosis,
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39 51 putting them at ultra-high risk for transition to psychotic disorder. At baseline and 1-year follow-
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41 52 up, participants report their symptoms, affective states and experiences for three consecutive
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43 53 months in short, daily questionnaires on their smartphone, which will be used to map individual
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45 54 networks. Network parameters, including the strength and directionality of symptom connections
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47 55 and centrality indices, will be estimated, and associated to individual differences in and within-
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49 56 individual progression through stages of clinical severity and functioning over the next three
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51 57 years.
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6 59 Ethics and dissemination: The study has been approved by the local medical ethical committee
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8 60 (ABR no. NL52974.042.15). The results of the study will be published in (inter)national peer-
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10 61 reviewed journals, presented at research, clinical and general public conferences. The results will
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12 62 assist in improving and fine-tuning dynamic models of psychopathology, stimulating both
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14 63 clinical and scientific progress.
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20 65 Trial registration:

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22 66 Netherlands Trial Register NTR6205, Registered 27 October 2016.

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24 67 <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6205>
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29 69 Strengths and limitations of this study:

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32 70 • One of the first studies examining the predictive potential of dynamic symptoms
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34 71 networks for the onset and progression of psychopathology
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36 72 • The study design allows considering within- and between-individual variation in
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38 73 symptomatology, both at the micro (day) and macro (year) level
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40 74 • A developmental, transdiagnostic approach is adopted; outcome measures include clinical
41
42 75 stage, diagnosis, symptoms of a broad range of disorders and functioning
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44 76 • With three yearly follow-ups, we may not capture all transitions to psychosis
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46 77 • The exploratory nature of the study warrants replication of the findings
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3 81 Words (main text): 4833
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83 Introduction

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

90
91 Current diagnostic systems in psychiatry are challenged by issues such as high levels of
92 comorbidity, clinical heterogeneity, non-specific treatment effects, and lack of diagnosis-specific
93 biological/ cognitive markers [8-12]. Despite this, traditional diagnoses still dominate psychiatric
94 research, hampering scientific progress. These diagnoses are based on clinical presentation of
95 adults with long-established illness [13], and classify individuals according to distinct diagnostic
96 labels [8] (e.g. schizophrenia or major depressive disorder). However, it is increasingly
97 acknowledged that psychopathology is expressed dimensionally, representing a quantitative as
98 well as qualitative deviations from mental health [8, 14-19]. In addition, it is increasingly
99 accepted that mental disorders do not emerge fully formed in adulthood but evolve gradually,
100 often manifesting for the first time already in adolescence [20, 21].

101
102 A model that was designed to capture this continuity of both severity and time is the clinical
103 staging model [22, 23]. This model describes psychopathology as ranging, through subsequent
104 but qualitatively different stages, from increased risk of mental illness at the lowest level through
105 progressive stages of severity, resulting in separable but overlapping syndromes at the highest

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3 106 levels [24, 25]. Stage 0 represents individuals at increased risk without symptoms; Stage 1a
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5 107 represents ‘help-seeking’ individuals with mild, non-specific symptoms; Stage 1b represents
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8 108 individuals with an ‘attenuated syndrome’, with moderate but subthreshold symptoms and
9
10 109 moderate functional decline; Stage 2 holds individuals with a first episode of a clinical,
11
12 110 ‘discrete’, disorder; Stage 3 holds individuals with persistent or recurrent illness [13, 22, 23] and
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14 111 Stage 4 represents individuals with chronic illness. This clinical staging model further
15
16 112 hypothesizes that psychopathological expression is more multi-dimensional, non-specific and
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18 113 more susceptible to intervention in early stages and becomes more crystallized, disorder specific
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20 114 and treatment-resistant in later stages [25]. This model offers a theoretical representation that
21
22 115 seems to fit better to the true nature and development of psychopathology [9-11, 26], and hence
23
24 116 may improve diagnostic accuracy. First investigations of the model seem promising, but more
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26 117 empirical research is needed [27]. It has been developed most extensively in the context of
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28 118 psychosis [23, 25, 28], but needs thorough empirical validation, since many questions still
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30 119 remain, e.g. about what drives progression through subsequent stages and how the thresholds
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32 120 between the stages should be defined exactly.
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41 122 The expression and development of early psychotic symptoms are highly variable [29-32] and
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43 123 difficult to predict [33, 34]. One reason for this is that many studies so far have focused on early
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45 124 psychotic symptoms as specific predictors of later schizophrenia. However, this approach may be
46
47 125 too narrow [25, 31, 35] because early psychotic symptoms are often transitory [36-38], also
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49 126 occur in the context of [6, 7, 39-41] and predict other mental disorders [33, 36, 42, 43], and vice
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51 127 versa [44-46]. High levels of comorbidity [47] and overlap of risk factors [48-51] also challenge
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53 128 the assumed independence of psychosis from other symptom domains. In addition, the
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3 129 information that is used to predict course and outcome is often based on cross-sectional
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5 130 assessment of symptoms and comparisons are often made at the group level. However,
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8 131 symptoms can vary substantially over time, both over short (i.e. days) and long intervals
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10 132 (months, years), within one individual, and can also cross diagnostic borders [52]. This means
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12
13 133 that the clinical picture can change, particularly in the early phase of a disorder [25]. These
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15 134 characteristics of psychopathology suggest that the 'static' model prediction may not be fit for
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17 135 the purpose. This is reflected in the modest accuracy and replicability of static prediction models
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20 136 in the psychosis prediction field [53-55].
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23 24 138 *The Mirorr study*

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27 139 The above-mentioned challenges may be overcome by taking a different approach towards the
28
29 140 conceptualization of psychopathology, its measurement and the way we model it. By taking a
30
31 141 more transdiagnostic approach, incorporating symptoms and experiences from multiple
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33 142 (psychotic and non-psychotic) domains, the narrow focus on the sole dimension of psychosis can
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36 143 be broadened. By modelling individual patterns of symptom patterns over time, a more
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38 144 developmental as well as a more personalized approach can be taken that, in addition, builds on a
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40 145 more detailed inventory of symptomatology compared to baseline (cross-sectional) assessment
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43 146 scores. Modelling the interconnectivity between symptoms by mapping individual symptom
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46 147 networks and patterns of co-occurrence in and over time could provide us with a better idea of
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48 148 how psychopathology develops and may give us clues on what processes may drive progression
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51 149 through subsequent clinical stages [56, 57]. To investigate these aspects, we designed the
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53 150 *Mapping Individual Routes of Risk and Resilience* (Mirorr) study.
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3 152 *Aims and hypotheses*
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5 153 With the Mirorr study, we aim to investigate the hypothesis of dynamic symptom networks as
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8 154 the basis of psychopathology in general and psychosis in particular. Furthermore, we aim to
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10 155 investigate the additional hypothesis of symptom networks as markers/indicators of progression
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12 156 of illness through successive clinical stages. Taking a broader, multidimensional and process-
13
14 157 oriented approach, we will examine how symptoms of multiple domains influence each other
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16 158 over time and across diagnostic boundaries, in interaction with environmental factors. More
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18 159 specifically, we hypothesize that different clinical stages will be characterized by different
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20 160 symptom networks. In addition, we expect that characteristics of these networks can predict
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22 161 progression through clinical stages. We will explore the predictive potential of several
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24 162 characteristics, such as the strength and directionality of symptom connections (see Figure 1) and
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26 163 centrality indices (information about the position of a symptom in the network).
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34 165 The Mirorr study is unique in its design and in its attempt to (i) bring together a network
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36 166 approach to psychopathology and the clinical staging model, (ii) take a broader perspective on
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38 167 mental illness by (a) taking a transdiagnostic approach towards symptomatology and (b) defining
39
40 168 outcome in more broadly in the context of clinical staging (incorporating both clinical and
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42 169 functional outcomes), and (iii) modelling individual symptom networks over time by using time-
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44 170 series data, enabling us to model more personalized pathways of psychopathological
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46 171 development.
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55 174 *A network approach to psychopathology*
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3 175 A focus on dynamic symptom networks requires an innovative approach to psychopathology.
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6 176 One of the currently promising alternative approaches comes from network theory. From this
7
8 177 network perspective, psychopathology, at a phenomenological level, is hypothesized to result
9
10 178 from interactions between symptoms [11, 58, 59]. Mental disorders are thus represented by sets
11
12 179 of symptoms, connected in networks by causal relations [11, 58] (see also Figure 1). These
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14 180 networks are dynamic and capture reciprocal influences between symptoms over time (e.g.,
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16 181 feedback loops). Importantly, symptoms are acknowledged as causal factors in
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18 182 psychopathological development: one symptom (e.g., anxiety) can cause another (e.g., paranoia).
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20 183 This is in sharp contrast with current dominant models that represent symptoms as independent
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22 184 indicators of underlying, latent constructs (e.g., schizophrenia). As stress is important in the
23
24 185 development of psychosis [60, 61], the sensitivity of symptom networks to risk-enhancing
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26 186 (trauma) and risk-reducing (coping, social support) factors [62, 63] also needs attention. The
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28 187 network approach has been successfully applied in other fields [64, 65], but is relatively novel in
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30 188 psychiatry, where it has been investigated mainly in common mental disorders [66], but not
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32 189 psychosis.
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41 *Outcome measures*

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43 192 Traditionally, research in the field of psychosis focuses mostly on transition from clinical high
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45 193 risk to a first episode of psychosis [67]. However, there is growing awareness that this may be
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47 194 arbitrary, especially in the context of a staging model that acknowledges expression of illness
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49 195 along a much broader severity spectrum. In addition, functional outcome is becoming more and
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51 196 more an important outcome of interest, as it has been shown that both clinical and functional
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53 197 outcome are important but not always congruent [68-70]. Working from a clinical staging
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3 198 perspective, important outcomes to investigate include therefore progression through clinical
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6 199 stages, functioning and need for care.

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10 201 Please insert Figure 1 here.

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15 203 *Objectives*

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17 204 Primary Objective:

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20 205 To investigate whether symptom networks can characterize different clinical stages and predict
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22 206 progression through subsequent stages, and whether there is a unique role of psychotic symptoms
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24 207 within these networks in a sample of young adults (18-35 years) with increased risk for
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27 208 psychosis. For this purpose, we examine both within-individual changes and between-individual
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29 209 differences in symptom networks and clinical stage.

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34 211 Secondary Objectives:

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36 212 1) To identify symptom networks that predict development of mental illness more accurately
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38 213 than current models that are based on a cross-sectional assessment of symptom severity, which
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40 214 have limited predictive accuracy;

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43 215 2) To examine how risk and resilience factors for stress influence symptom networks. Examples
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45 216 of risk factors are daily stress and early trauma; examples of resilience factors are coping
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47 217 strategies, social support, physical activity and the experience of positive affect.

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55 220 **Methods and analysis**

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3 221 *Study design*
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5 222 This study combines idiographic (within-person) and nomothetic (between-person) observational
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8 223 study designs. The nomothetic aspect of the study is captured by questionnaire and interview
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10 224 data at baseline and three yearly follow measurement waves. Among other things,
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12 225 symptomatology, functioning and need for care will be assessed (outcome measures), as well as
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14 226 risk and protective factors. The idiographic aspect is captured by diary assessments at baseline
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16 227 and the first follow-up wave. During the diary periods, participants will complete a diary
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18 228 questionnaire daily for a period of 90 days on their smartphone, regarding symptoms, emotions,
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20 229 functioning and stress. These diary data are used to map individual symptom networks. For the
21
22 230 second diary period, participants can also opt to keep continuing the questionnaire follow-ups,
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24 231 but not have a second diary period. A flowchart of the study is presented in Figure 2.
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36 233 Please insert Figure 2 here.
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36 235 *Study population*
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38 236 The total sample comprises of 175 individuals of 18-35 years, whereof 100 will enter the main
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40 237 study (i.e. the daily diary study and the yearly follow-ups). For the main study, there will be four
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42 238 subsamples, all n=25 (Figure 3) with each subgroup having an increasingly more severe
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44 239 psychopathological level and thus representing subsequent clinical stages. For subsample 1
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46 240 (lowest level of psychopathology and thus lowest clinical stage), 100 individuals will be
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48 241 randomly selected from the general population in the North of the Netherlands and administered
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50 242 the Community Assessment of Psychic Experiences (CAPE) [71]. Of all the respondents who
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52 243 meet the inclusion and exclusion criteria of the study, the highest scoring quartile will be
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3 244 included in the main study. For subsamples 2-4, individuals will be recruited from mental health
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5 245 care institutions in the four Northern provinces in The Netherlands. For all individuals who are
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8 246 referred to mental health care, psychotic symptoms are routinely screened by means of, among
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10 247 other things, the Prodromal Questionnaire (PQ) [72]. If the score on the PQ is 6 or higher, the
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12 248 Comprehensive Assessment of At Risk Mental State (CAARMS) [73] is administered as well.
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14 249 With these scores it is determined for which subsample (2-4, explained below) eligible subjects
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16 250 will be recruited, where a higher subsample indicates higher levels of psychopathology.
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22 252 Please insert Figure 3 here.
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27 254 In order to be eligible to participate in the study, subjects must meet all of the following criteria:
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29 255 1) age between 18 and 35 years, 2) read and speak Dutch fluently, 3) capable of following the
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31 256 research procedures, 4) provide Informed Consent. In addition, participants of subsample 1
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33 257 should *not* be in clinical care for mental health at the moment of screening. In contrast,
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35 258 participants of subsample 2-4 *should* currently be in clinical care for mental health. In addition,
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37 259 participants of subsample 2 should have mild, non-psychotic psychopathology, as evidenced by a
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39 260 score below 6 on the PQ, participants of subsample 3 should have mild psychopathology
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41 261 including subclinical psychotic symptoms, as evidenced by a score of or above 6 on the PQ, but
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43 262 are not at ultra-high risk (UHR) for psychosis, as indexed by the CAARMS. Finally, participants
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45 263 of subsample 4 should be at UHR for psychosis, as indexed by the CAARMS. Exclusions criteria
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47 264 are: 1) a history of or current psychotic episode, according to the Diagnostic and Statistical
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49 265 manual of Mental Disorders-IV (DSM-IV) criteria; 2) significant hearing or visual problems
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51 266 impairments; 3) pregnancy, as stated on a general health questionnaire.
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6 268 *Procedure*7
8 269 Recruitment

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10 270 To recruit subsample 1, the study will be announced at several university sites, public places in
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12 271 Groningen, and social media (start recruitment: September 2015). Interested individuals can
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14 272 contact the researchers by phone or e-mail for more information. They will then be sent an
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16 273 information letter, flyer, informed consent form and the initial screenings questionnaires. After
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18 274 receiving the completed screening questionnaires and informed consent forms, the 25 (out of
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20 275 100) individuals with the highest CAPE scores will be invited to participate in the main study
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22 276 (first inclusion: December 2015). For subsample 2-4, individuals will be recruited from mental
23
24 277 health care institutions in four northern Dutch provinces (first inclusion: April 2016). To which
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26 278 subsample they will be recruited is determined using the instruments described under study
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28 279 population. For these sites where patients give their consent for receiving information about
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30 280 ongoing research projects, a package containing detailed information on the study (information
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32 281 letter and flyer), along with screening questionnaires and an informed consent form will be send
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34 282 to potential participants. Interested individuals can fill out and return requested forms (including
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36 283 informed consent form). After receiving the requested forms, an individual's therapist will be
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38 284 consulted about several exclusion criteria. For these sites where participants do not give consent
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40 285 in advance, the individual's clinical worker will be provided a package containing detailed
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42 286 information on the study (information letter and flyer), along with screening questionnaires and
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44 287 an informed consent form. The clinical worker will pre-screen his/her client on the exclusion
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46 288 criteria of the study and hand over the package if he/she fits the profile of the study. Study
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3 289 participants can continue their therapy and medical treatment as usual; they will be asked to
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6 290 register any changes in medication or treatment during the daily ambulatory assessments.
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10 292 Screening

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12 293 The information package that interested individuals receive contains an information letter, two
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15 294 screening questionnaires and an informed consent form. All potential participants can ask
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17 295 questions before completing informed consent form or the screening questionnaires. As
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20 296 mentioned in the information letter, in case subjects should decide to participate, they should fill
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22 297 out and send back these questionnaires and the informed consent form. This consent form covers
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24 298 the baseline ambulatory assessment period and the yearly follow-up assessments (three in total).

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27 299 On this consent form permission will be asked to re-invite subjects for the follow-up ambulatory
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29 300 assessment period, for which they have to complete a separate consent form (one year later).

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31 301 Also, permission will be asked to use data from the psychiatric case register of the North of the
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33
34 302 Netherlands. The first screening questionnaire is a screening questionnaire on general health,
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36 303 containing questions on demographics, health complaints (such as visual or hearing
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38 304 impairments), pregnancy, drug and alcohol use, medication use, and mental health problems.

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41 305 This will be used to screen on exclusion criteria. The second screening questionnaire is the
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44 306 CAPE. This instrument is used to screen individuals recruited from the general population
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46 307 (subsample 1) on psychotic experiences but will be administered to all participants to enable
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48 308 group comparisons on the level of subclinical psychotic experiences. The highest scoring quartile
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50 309 (n=25) will subsequently be included in the main study. Subjects will have one week to decide
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52 310 about participation.

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3 312 Baseline interview and ambulatory assessments (year one)
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6 313 If subjects are eligible to enter the study and agree to participate, they will be invited (by
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8 314 telephone or e-mail) for an introduction interview at the University Medical Centre Groningen. A
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10 315 few days before the interview, self-report questionnaires will be administered via email (see data
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12 316 management for more information). The questionnaires assess symptomatology, functioning,
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14 317 clinical stage, and factors of risk and resilience. During the interview, the study will be explained
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16 318 to them in detail and a diagnostic psychiatric interview will be held. If in an exceptional case the
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18 319 participant does not possess a smartphone, this will be provided to the participant during the
19
20 320 study period. An appointment for an end-of-study interview will be planned. Also, the
21
22 321 participants will be asked to designate suitable moments at which the researcher can call him/her
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24 322 to inquire on the progression of the study and to help with any problems the participant may
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26 323 experience.
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34 325 The participants then start completing the electronic daily diary for three months. Every evening,
35
36 326 they receive a text message with a link which directs them to a web-based diary questionnaire in
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38 327 a secure environment. Measurements are always in the evening, asking about the past day; exact
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40 328 times can vary per person (but not per day) and are fixed according to the participant's wishes.
41
42 329 However, *all* participants have 24 hours between each measurement point. For example,
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44 330 participant A will always receive her text message at 22.00 and participant B always at 21.15. A
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46 331 window of one and a half hour will be allowed to fill in the diary, and reminder messages will be
47
48 332 send every half hour. Short questions will be presented on sequential screens, which are mainly
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50 333 answered using visual analogue scales. During the research period, participants are also provided
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52 334 a paper log, in which they can note any unusual events, start of or changes in medication use and
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3 335 problems they encounter with the research procedures. The researchers will telephone the
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6 336 participants six times during the study period (every other week), to motivate the participant,
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8 337 answer questions about the study procedures and provide technical help. They will also be
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10 338 available by telephone and e-mail if participants need help at other moments.
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15 340 During the end-of-ambulatory-assessment (3 months after baseline) interview participants will
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17 341 fill out an online questionnaire battery once more, and report on any changes in medical
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19 342 treatment. Furthermore, they will also be asked to comment on the data collection and the study
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21 343 in general. We will use this information to check whether the study affected their thoughts and
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23 344 behaviours in any way, whether there had been special events that might have affected the data
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25 345 collected.
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31 347 Follow-up assessments
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34 348 One, two and three years after baseline, all participants will receive questionnaires about
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36 349 functioning and clinical stage via email. The participants will be able to fill these in at home.
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38 350 Shortly after filling in the questionnaires, participants will be interviewed by telephone or face-
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40 351 to-face at one of our research facilities, depending on their preferences, to establish the
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42 352 presence/absence of psychiatric disorders with a diagnostic interview. In addition, to distinguish
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44 353 individuals in clinical stage 1a from individuals in clinical stage 1b (all individuals with a score
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46 354 of 6 or higher on the PQ-16), data from the CAARMS interview is needed. Participants will be
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48 355 reminded about the follow-up assessments a few weeks before the actual follow-up by means of
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50 356 an information letter.
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3 358 Follow-up ambulatory assessment period (year two)
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5 359 In the aforementioned information letter, participants will also read information about a second
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8 360 ambulatory assessment period that they can enrol in. If they are interested, they are invited for
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10 361 another introduction interview (given that they still fulfil the in- and exclusion criteria as
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12 362 evidenced by their answers to an online version of a general health questionnaire). This interview
13
14 363 is similar to the introduction interview at baseline (i.e., questionnaire battery and procedures). An
15
16 364 exception is that questionnaires about symptomatology, functioning and clinical stage will not be
17
18 365 administered, because they have been covered already by the usual follow-up assessments.
19
20 366 Participants then start their second three-month period of ambulatory assessments one year after
21
22 367 the first diary period. The end-of-ambulatory-assessment interview will take place, again with
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24 368 similar questionnaires to the one held at baseline.
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32 370 *Instruments*

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34 371 A complete overview of the instruments used throughout the study is presented in Table 1.
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39 373 Please insert Table 1 here.
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42 43 375 *Diary measures*

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45 376 The items assessed in the daily questionnaires will be used to model individual networks of
46
47 377 symptoms, experiences and emotions. Items included in the dairy questionnaires were chosen
48
49 378 from a transdiagnostic perspective and cover a broad range of feelings and experiences that are
50
51 379 characteristic for (subclinical) psychotic experiences, depression, anxiety, mania, obsessive
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53 380 compulsive behaviour and anger. These disorders are known for the co-occurrence of psychotic
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3 381 symptoms [6, 7] and comorbidity [47]. For the complete item list, see Additional file 1, Table
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10 384 Positive psychotic experiences can be divided into five categories, namely paranoia, delusions,
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12 385 hallucinations, megalomania, and paranormal beliefs [74]. Because paranormal beliefs are often
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15 386 stable over time, we will include items covering the first four categories. Negative symptoms of
16
17 387 psychosis will be covered by items about flattened affect (e.g., anhedonia, low motivation, social
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20 388 withdrawal), which resemble closely the negative symptoms of the CAPE. Most items are
21
22 389 adopted from previous ESM studies [75-77], and all items are adapted for daily use.

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27 391 Symptoms of depression will be measured using items that correspond closely to the patient
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29 392 health questionnaire (PHQ-9) [78], a self-administered questionnaire for screening and
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31 393 measuring the severity of depression. Anxiety symptoms will be measured using items that
32
33 394 correspond closely to the Hospital Anxiety and Depression Scales – Anxiety (HADS-A) [79].
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35 395 Mania, obsessive compulsive behaviour and anger are measured with items that correspond
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37 396 closely to items from the DSM-V – screener for the corresponding clinical disorders [80].
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43 398 Positive and negative mood states over the past day will be measured with 12 items from the
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45 399 circumplex model of affect [81, 82]. Momentary affect will be measured with an item for
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47 400 valence (“I feel unpleasant – pleasant”) and activation (“I feel aroused/activated – quiet/still”) at
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49 401 the beginning of each diary entry. Other items cover sleep, daily activities and situations that
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51 402 may influence psychiatric symptoms, such as positive and negative events, social interactions,
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53 403 coping behaviour, physical activity and drug use.
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6 405 Follow-up measures
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8 406 Important outcomes that are linked to the above described network characteristics are
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10 407 (progression through) clinical stages, functioning and need for care. Progression through clinical
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12 408 stages will be assessed with the PQ-16, the CAPE and the CAARMS, the Symptom Check List
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14 409 (SCL-90) [83] and the Schedules for Clinical Assessment in Neuropsychiatry, short version
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16 410 (mini-SCAN) [84]. Social functioning will be assessed using the Groningse Vragenlijst voor
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18 411 Sociaal Gedrag (GVSG-45) [85] and the Flourishing Scale [86]. Need for care will be assessed
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20 412 using self-reported information on care use. Additionally, need for care will be assessed by
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22 413 linking data from the psychiatric case registry to our sample when approved by the participant
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24 414 (as stated on the informed consent form). Specifically, the frequency and type of care use
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26 415 throughout the study period will be obtained.
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32 416 Assessments pre- and post-daily diary period(s)

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34 417 Before and after the daily diary assessments, several questionnaires will be administered to
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36 418 assess symptomatology, functioning and several risk and resilience factors. Psychotic symptoms
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38 419 will be assessed with the CAPE; depression and anxiety symptoms with the Depression Anxiety
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40 420 and Stress Scale (DASS) [87]; mania symptoms with the Altman Self-Rating Mania Scale
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42 421 (ASRM-NL) [88], social support with the Social Support List (SLL) [89]; resilience with the
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44 422 Brief Resilience Scale (BRS) [90] and coping style with the Utrechtse Coping Lijst (UCL) [91].
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46 423 Furthermore, physical activity levels will be tracked with an accelerometer, the ActiCal®
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48 424 (Respironics, Bend, OR, USA), during the first two weeks of the second diary period. Output of
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3 426 this instrument will be presented as Energy Expenditure and Metabolic Equivalent of Task. The
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6 427 physical activity measurements are added to serve as a pilot study, and are not obligatory.

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10 429 At baseline, sleep habits will be assessed with the Munich Chronotype Questionnaire (MCTQ)
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12 430 [92] to optimize the diary assessment process. Also, potential confounders such as smoking,
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14 431 alcohol/drug consumption, socio-economic status, Body Mass Index will be registered by means
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16 432 of a general health questionnaire. In addition, stressful life events will be assessed, using the list
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18 433 of threatening experiences [93]. Finally, pertaining to subgroup 4 only, social cognition will be
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20 434 assessed using the Faux Pas Task [94] and bonding with parents will be assessed with the
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22 435 Inventory of Parent and Peer Attachment (IPPA) [95, 96]. These factors may be of importance in
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24 436 determining a transition from an UHR status to psychosis.

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34 439 *Data analysis plan*

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36 440 To map individual symptom networks of day-to-day symptom levels, multivariate time-series
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38 441 analysis will be employed on each individual's time series data. Specifically, vector
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40 442 autoregression (VAR) models will be applied [97]. These models are particularly suited for
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42 443 investigating the temporal dynamics between two or more variables. The resulting associations
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44 444 between symptoms will subsequently be presented as networks, and network parameters will be
45
46 445 estimated. These include (but are not limited to) the strength and directionality of symptom
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48 446 connections (see Figure 1) and centrality indices (information about the position of a symptom in
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50 447 the network). Next, symptom networks will be compared (i) across different subgroups of
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52 448 severity and (ii) when the second diary period is completed, within each individual.

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6 450 In addition, a data-driven approach will be used to identify individuals with similar symptom
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8 451 network characteristics by (1) qualitative network comparison, (2) quantitative comparison of
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10 452 centrality indices [98, 99], and (3) longitudinal mixture models [100]. These subgroups will then
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12 453 be compared on their levels of symptomatology and functioning and on course of
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14 454 symptomatology over time. Furthermore, the predictive value of the network parameters will be
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16 455 compared to the predictive value of usual predictors of illness course, namely cross-sectionally
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18 456 assessed level of (subclinical) psychotic pathology. Specifically, sensitivity and specificity of
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20 457 these network characteristics can be compared to sensitivity and specificity of baseline
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22 458 subclinical levels of psychotic symptoms (CAPE) and general psychopathology (SCL-90).
23
24 459 Finally, risk and resilience factors, such as stressful events, social interactions, physical activity,
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26 460 coping and resilience, may also influence symptoms and, importantly, their dynamics in the
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28 461 network, but may do so differently in individuals with good or poor clinical and functional
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30 462 outcome. The role of these factors will be addressed by including them in individual network
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32 463 analyses to examine their direct and indirect impact on symptomatology and each other.
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34 464 To control for potential confounding effects of demographic factors, such as sex, age and social
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36 465 economic status, these variables will be added as covariates to all group level analyses.
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46 467 Based on previous work [101, 102], we expect no more than 10% missing data. Missing values
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48 468 will be imputed with expectation-maximization imputation, following special recommendations
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50 469 for time-series datasets [103]. A (two-sided) p-value of 0.05 is applied for statistical testing.
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55 471 *Sample size and power*
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3 472 Within-person analyses: constructing individual symptom networks
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5 473 Exact sample size calculations are not possible in studies using VAR, as it is typically unclear in
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8 474 such studies what effect size can be expected. This is because the direction of causality and the
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10 475 number of lagged influences in the system under investigation are usually unknown and
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12 476 bidirectional and feedback effects can be present as well [97]. However, as previous work from
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14 477 our group [101, 104, 105] and work of others [106] suggests, 60-90 measurements suffice to
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16 478 reliably identify reciprocal associations between multiple variables.
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22 480 Between-person analyses: associating symptom networks to clinical stage
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24 481 In the between-person analyses, the data have a multilevel structure. Therefore, the unilevel
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26 482 equivalent of the multilevel sample size [107] was taken to calculate the power, assuming a
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28 483 conservative intraclass-correlation of 0.8. Assuming differences of 0.05 in mean coefficients (s.d.
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30 484 = 0.07) between the different groups [108], the proposed study has a power of 0.8 (to detect
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32 485 significant differences at $p < 0.05$). Subgroups of $N=25$ are large enough to take into account
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34 486 effects of several covariates [109].
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40 41 488 **Ethics and dissemination** 42

43 489 This study has been approved by the medical ethical committee of the University Medical Centre
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45 490 Groningen (UMCG), Groningen, The Netherlands (registration number MEC no. 2015/159,
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47 491 ABR no. NL52974.042.15). The study will be conducted in accordance with the Helsinki
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49 492 Declaration, meaning that participation is voluntary and written informed consent will be
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52 493 obtained.
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3 495 An online outcome monitoring system, called RoQua (www.roqua.nl) is used for data collection
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6 496 and data storage, to which only designated researchers have access via the use of passwords
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8 497 combined with google authentication. Participants have access to the questionnaires via a link in
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10 498 their e-mail inbox. The safety of this system is guaranteed by the UMCG (an ‘In Control
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12 499 Statement’ is available on request). Data management is also organized according to UMCG
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14 500 standards, including a strict separation of identifying patient data (name, date of birth etc.) and
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16 501 the anonymous datasets available for the researchers.
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22 503 Data gathering was not completed when this manuscript was submitted. After the publication of
23
24 504 this study’s main results, the data obtained by this study will become available on reasonable
25
26 505 request. Requests should be sent to j.t.w.wigman@umcg.nl with the topic name MIRORR data.
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28 506 The results of the study will be published in (inter)national peer-reviewed journals, presented at
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30 507 research, clinical and general public conferences.
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35 509 **Conclusion**

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38 510 Conceptualization of psychopathology in terms of (i) clinical staging (at macro level) and (ii)
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40 511 dynamic, individual symptom networks (at a more micro level), which is the purpose of this
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42 512 study, represents a promising avenue to tackle both scientific and clinical problems. Improving
43
44 513 our understanding of the factors driving the development of psychopathology by investigating
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46 514 how symptoms influence each other will enhance our ability to identify valid phenotypes to
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48 515 predict onset of (psychotic) mental disorders and to link with other relevant information (e.g.,
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50 516 genetic or endophenotypic variation). In addition, a better understanding of why psychotic
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52 517 symptoms can lead to a need for care in some, but resolve spontaneously in others, will help
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3 518 mental health professionals to adequately recognize the early needs of individuals who are likely
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5 519 to develop mental illness or functional impairments.
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9
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11
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33 530 **References**

- 34
35 531 1 van Os J, Kapur S. Schizophrenia, *The Lancet* 2009;374:635-45.
36
37 532 2 Eaton WW, Martins SS, Nestadt G, et al. The burden of mental disorders, *Epidemiol Rev*
38 533 2008;30:1-14.
39
40
41 534 3 McCrone PR, Dhanasiri S, Patel A, et al. Paying the price: the cost of mental health care in
42 535 England to 2026: King's Fund 2008.
43
44
45 536 4 Nationaal Kompas Volksgezondheid. Psychisch functioneren: Zijn er verschillen tussen
46 537 Nederland en andere landen? Preventie gericht op psychisch functioneren van jeugd. .
47
48
49 538 5 Van Os J, Linscott RJ, Myin-Germeys I, et al. A systematic review and meta-analysis of the
50 539 psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of
51 540 psychotic disorder, *Psychol Med* 2009;39:179-95.
52
53 541 6 Wigman J, van Nierop M, Vollebergh WA, et al. Evidence that psychotic symptoms are
54 542 prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity--
55 543 implications for diagnosis and ultra-high risk research, *Schizophr Bull* 2012;38:247-57.
56
57
58
59
60

- 1
2
3 544 7 Wigman J, van Os J, Abidi L, et al. Subclinical psychotic experiences and bipolar spectrum
4 545 features in depression: association with outcome of psychotherapy, *Psychol Med* 2014;44:325-
5 546 36.
- 7
8 547 8 Kendell R, Jablensky A. Distinguishing between the validity and utility of psychiatric
9 548 diagnoses, *Am J Psychiatry* 2003.
- 11
12 549 9 Widiger TA. A dimensional model of psychopathology, *Psychopathology* 2005;38:211-4.
- 14
15 550 10 Widiger TA, Samuel DB. Diagnostic categories or dimensions? A question for the Diagnostic
16 551 and statistical manual of mental disorders--, *J Abnorm Psychol* 2005;114:494.
- 17
18 552 11 Kendler KS, Zachar P, Craver C. What kinds of things are psychiatric disorders? *Psychol Med*
19 553 2011;41:1143-50.
- 21
22 554 12 Kupfer DJ, First MB, Regier DA. A research agenda for DSM V: American Psychiatric Pub
23 555 2008.
- 25
26 556 13 Hickie IB, Scott J, McGorry PD. Clinical staging for mental disorders: a new development in
27 557 diagnostic practice in mental health, *Med J Aust* 2013;198:461-2.
- 28
29 558 14 Strauss JS. Hallucinations and delusions as points on continua function: Rating scale
30 559 evidence, *Arch Gen Psychiatry* 1969;21:581-6.
- 32
33 560 15 Haslam N, Holland E, Kuppens P. Categories versus dimensions in personality and
34 561 psychopathology: a quantitative review of taxometric research, *Psychol Med* 2012;42:903-20.
- 35
36 562 16 Kendler KS, Gardner Jr CO. Boundaries of major depression: an evaluation of DSM-IV
37 563 criteria, *Am J Psychiatry* 1998.
- 39
40 564 17 Angst J, Gamma A, Benazzi F, et al. Toward a re-definition of subthreshold bipolarity:
41 565 epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania, *J*
42 566 *Affect Disord* 2003;73:133-46.
- 44
45 567 18 Carter RM, Wittchen H, Pfister H, et al. One - year prevalence of subthreshold and threshold
46 568 DSM - IV generalized anxiety disorder in a nationally representative sample, *Depress Anxiety*
47 569 2001;13:78-88.
- 49
50 570 19 Krueger RF, Piasecki TM. Toward a dimensional and psychometrically-informed approach to
51 571 conceptualizing psychopathology, *Behav Res Ther* 2002;40:485-99.
- 52
53 572 20 Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during
54 573 adolescence? *Nature Reviews Neuroscience* 2008;9:947-57.
- 55
56
57
58
59
60

- 1
2
3 574 21 Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions
4 575 of DSM-IV disorders in the National Comorbidity Survey Replication, *Arch Gen Psychiatry*
5 576 2005;62:593-602.
- 7
8 577 22 McGorry PD, Hickie IB, Yung AR, et al. Clinical staging of psychiatric disorders: a heuristic
9 578 framework for choosing earlier, safer and more effective interventions, *Aust N Z J Psychiatry*
10 579 2006;40:616-22.
- 12
13 580 23 McGorry PD. Issues for DSM-V: clinical staging: a heuristic pathway to valid nosology and
14 581 safer, more effective treatment in psychiatry, *Am J Psychiatry* 2007.
- 16
17 582 24 Wigman JT, van Os J, Thiery E, et al. Psychiatric diagnosis revisited: towards a system of
18 583 staging and profiling combining nomothetic and idiographic parameters of momentary mental
19 584 states, *PLoS One* 2013;8:e59559.
- 21
22 585 25 McGorry P, van Os J. Redeeming diagnosis in psychiatry: timing versus specificity, *Lancet*
23 586 2013;381:343-5.
- 25
26 587 26 Hyman SE. The diagnosis of mental disorders: the problem of reification, *Annual review of*
27 588 *clinical psychology* 2010;6:155-79.
- 28
29 589 27 McGorry P, Keshavan M, Goldstone S, et al. Biomarkers and clinical staging in psychiatry,
30 590 *World Psychiatry* 2014;13:211-23.
- 32
33 591 28 McGorry PD, Killackey E, Yung AR. Early intervention in psychotic disorders: detection and
34 592 treatment of the first episode and the critical early stages, *Med J Aust* 2007;187:S8-10.
- 35
36 593 29 Scott J, Leboyer M, Hickie I, et al. Clinical staging in psychiatry: a cross-cutting model of
37 594 diagnosis with heuristic and practical value, *Br J Psychiatry* 2013;202:243-5.
- 39
40 595 30 Keshavan MS, DeLisi LE, Seidman LJ. Early and broadly defined psychosis risk mental
41 596 states, *Schizophr Res* 2011;126:1-10.
- 42
43 597 31 Fusar-Poli P, Yung A, McGorry P, et al. Lessons learned from the psychosis high-risk state:
44 598 towards a general staging model of prodromal intervention, *Psychol Med* 2014;44:17-24.
- 46
47 599 32 Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features
48 600 and conceptualization, *Schizophr Res* 2009;110:1-23.
- 49
50 601 33 Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition
51 602 outcomes in individuals at high clinical risk, *Arch Gen Psychiatry* 2012;69:220-9.
- 53
54 603 34 Lin A, Nelson B, Yung A. 'At-risk' for psychosis research: where are we heading?
55 604 *Epidemiology and psychiatric sciences* 2012;21:329-34.

- 1
2
3 605 35 van Os J. The dynamics of subthreshold psychopathology: implications for diagnosis and
4 606 treatment, *Am J Psychiatry* 2013.
- 607 36 Kaymaz N, Drukker M, Lieb R, et al. Do subthreshold psychotic experiences predict clinical
608 outcomes in unselected non-help-seeking population-based samples? A systematic review and
609 meta-analysis, enriched with new results, *Psychol Med* 2012;42:2239-53.
- 610 37 Velthorst E, Nieman D, Klaassen R, et al. Three - year course of clinical symptomatology in
611 young people at ultra high risk for transition to psychosis, *Acta Psychiatr Scand* 2011;123:36-42.
- 612 38 Zammit S, Kounali D, Cannon M, et al. Psychotic experiences and psychotic disorders at age
613 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study,
614 *Am J Psychiatry* 2013.
- 615 39 Kelleher I, Keeley H, Corcoran P, et al. Clinicopathological significance of psychotic
616 experiences in non-psychotic young people: evidence from four population-based studies, *Br J*
617 *Psychiatry* 2012;201:26-32.
- 618 40 van Rossum I, Dominguez MD, Lieb R, et al. Affective dysregulation and reality distortion: a
619 10-year prospective study of their association and clinical relevance, *Schizophr Bull*
620 2011;37:561-71.
- 621 41 Wigman J, Lin A, Vollebergh W, et al. Subclinical psychosis and depression: co-occurring
622 phenomena that do not predict each other over time, *Schizophr Res* 2011;130:277-81.
- 623 42 Werbeloff N, Drukker M, Dohrenwend BP, et al. Self-reported attenuated psychotic
624 symptoms as forerunners of severe mental disorders later in life, *Arch Gen Psychiatry*
625 2012;69:467-75.
- 626 43 Addington J, Cornblatt BA, Cadenhead KS, et al. At clinical high risk for psychosis: outcome
627 for nonconverters, *Am J Psychiatry* 2011;168:800-5.
- 628 44 Yung AR, Phillips LJ, Yuen HP, et al. Psychosis prediction: 12-month follow up of a high-
629 risk ("prodromal") group, *Schizophr Res* 2003;60:21-32.
- 630 45 Yung AR, Phillips LJ, Yuen HP, et al. Risk factors for psychosis in an ultra high-risk group:
631 psychopathology and clinical features, *Schizophr Res* 2004;67:131-42.
- 632 46 Demjaha A, Valmaggia L, Stahl D, et al. Disorganization/cognitive and negative symptom
633 dimensions in the at-risk mental state predict subsequent transition to psychosis, *Schizophr Bull*
634 2012;38:351-9.
- 635 47 Kessler RC, Birnbaum H, Demler O, et al. The prevalence and correlates of nonaffective
636 psychosis in the National Comorbidity Survey Replication (NCS-R), *Biol Psychiatry*
637 2005;58:668-76.

- 1
2
3 638 48 Breetvelt EJ, Boks MP, Numans ME, et al. Schizophrenia risk factors constitute general risk
4 639 factors for psychiatric symptoms in the population, *Schizophr Res* 2010;120:184-90.
5
6
7 640 49 Weiser M, van Os J, Davidson M. Time for a shift in focus in schizophrenia: from narrow
8 641 phenotypes to broad endophenotypes, *Br J Psychiatry* 2005;187:203-5.
9
10 642 50 Craddock N, O'Donovan MC, Owen MJ. Psychosis genetics: modeling the relationship
11 643 between schizophrenia, bipolar disorder, and mixed (or "schizoaffective") psychoses, *Schizophr*
12 644 *Bull* 2009;35:482-90.
13
14
15 645 51 Hill SK, Reilly JL, Harris MS, et al. A comparison of neuropsychological dysfunction in first-
16 646 episode psychosis patients with unipolar depression, bipolar disorder, and schizophrenia,
17 647 *Schizophr Res* 2009;113:167-75.
18
19
20 648 52 Bystritsky A, Nierenberg A, Feusner J, et al. Computational non-linear dynamical psychiatry:
21 649 a new methodological paradigm for diagnosis and course of illness, *J Psychiatr Res*
22 650 2012;46:428-35.
23
24
25 651 53 Strobl EV, Eack SM, Swaminathan V, et al. Predicting the risk of psychosis onset: advances
26 652 and prospects, *Early intervention in psychiatry* 2012;6:368-79.
27
28 653 54 Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive
29 654 state-of-the-art review, *JAMA psychiatry* 2013;70:107-20.
30
31
32 655 55 Barnaby N, McGorry PD, Wichers M, et al. Moving from static to dynamic models of the
33 656 onset of mental disorder, In press.
34
35 657 56 Nelson B, McGorry PD, Wichers M, et al. Moving From Static to Dynamic Models of the
36 658 Onset of Mental Disorder: A Review, *Jama psychiatry* 2017;74:528-34.
37
38
39 659 57 Guloksuz S, Pries L, van Os J. Application of network methods for understanding mental
40 660 disorders: pitfalls and promise, *Psychol Med* 2017:1-10.
41
42
43 661 58 Borsboom D, Cramer AO. Network analysis: an integrative approach to the structure of
44 662 psychopathology, *Annual review of clinical psychology* 2013;9:91-121.
45
46 663 59 Borsboom D, Cramer AO, Schmittmann VD, et al. The small world of psychopathology, *PloS*
47 664 *one* 2011;6:e27407.
48
49
50 665 60 van Os J, Kenis G, Rutten BP. The environment and schizophrenia, *Nature* 2010;468:203-12.
51
52 666 61 Wigman J, Kelleher I, Devlin N, et al. Coping as a moderating factor between psychotic
53 667 symptoms and functioning in adolescents with mental illness. 2013;22:S108-9.
54
55 668 62 Roe D, Yanos PT, Lysaker PH. Coping with psychosis: an integrative developmental
56 669 framework, *J Nerv Ment Dis* 2006;194:917-24.
57
58
59
60

- 1
2
3 670 63 Yanos P, Moos R. Determinants of functioning and well-being among individuals with
4 671 schizophrenia: an integrated model, *Clin Psychol Rev* 2007;27:58-77.
- 6
7 672 64 Barabási A, Frangos J. *Linked: the new science of networks* science of networks: Basic
8 673 Books 2014.
- 10
11 674 65 Barabási A. *Bursts: the hidden patterns behind everything we do, from your e-mail to bloody*
12 675 *crusades*: Penguin 2010.
- 14
15 676 66 Schmittmann VD, Cramer AO, Waldorp LJ, et al. Deconstructing the construct: A network
16 677 perspective on psychological phenomena, *New Ideas Psychol* 2013;31:43-53.
- 18
19 678 67 Yung AR, Nelson B, Thompson A, et al. The psychosis threshold in Ultra High Risk
20 679 (prodromal) research: is it valid? *Schizophr Res* 2010;120:1-6.
- 22
23 680 68 Oorschot M, Lataster T, Thewissen V, et al. Symptomatic remission in psychosis and real-life
24 681 functioning, *Br J Psychiatry* 2012;201:215-20.
- 26
27 682 69 Verma S, Subramaniam M, Abdin E, et al. Symptomatic and functional remission in patients
28 683 with first - episode psychosis, *Acta Psychiatr Scand* 2012;126:282-9.
- 30
31 684 70 Wunderink L, Nieboer RM, Wiersma D, et al. Recovery in remitted first-episode psychosis at
32 685 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment
33 686 strategy: long-term follow-up of a 2-year randomized clinical trial, *JAMA psychiatry*
34 687 2013;70:913-20.
- 36
37 688 71 Konings M, Bak M, Hanssen M, et al. Validity and reliability of the CAPE: a self - report
38 689 instrument for the measurement of psychotic experiences in the general population, *Acta*
39 690 *Psychiatr Scand* 2006;114:55-61.
- 41
42 691 72 Ising HK, Velting W, Loewy RL, et al. The validity of the 16-item version of the Prodromal
43 692 Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-
44 693 seeking population, *Schizophr Bull* 2012;38:1288-96.
- 46
47 694 73 Yung AR, Yung AR, Pan Yuen H, et al. Mapping the onset of psychosis: the comprehensive
48 695 assessment of at-risk mental states, *Aust N Z J Psychiatry* 2005;39:964-71.
- 50
51 696 74 Wigman JT, Vollebergh WA, Raaijmakers QA, et al. The structure of the extended psychosis
52 697 phenotype in early adolescence--a cross-sample replication, *Schizophr Bull* 2011;37:850-60.
- 54
55 698 75 Oorschot M, Kwapil T, Delespaul P, et al. Momentary assessment research in psychosis.
56 699 *Psychol Assess* 2009;21:498.
- 58
59 700 76 Myin-Germeys I, Marcelis M, Krabbendam L, et al. Subtle fluctuations in psychotic
60 701 phenomena as functional states of abnormal dopamine reactivity in individuals at risk, *Biol*
702 *Psychiatry* 2005;58:105-10.

- 1
2
3 703 77 Wigman JT, Collip D, Wichers M, et al. Altered transfer of momentary mental states
4 704 (ATOMS) as the basic unit of psychosis liability in interaction with environment and emotions,
5 705 *PLoS One* 2013;8:e54653.
- 7
8 706 78 Kroenke K, Spitzer RL, Williams JB. The Phq - 9, *Journal of general internal medicine*
9 707 2001;16:606-13.
- 11
12 708 79 Zigmond AS, Snaith RP. The hospital anxiety and depression scale, *Acta Psychiatr Scand*
13 709 1983;67:361-70.
- 15
16 710 80 American Psychiatric Association. Diagnostic and statistical manual of mental disorders
17 711 (DSM-5®): American Psychiatric Pub 2013.
- 19
20 712 81 Yik M, Russell JA, Steiger JH. A 12-point circumplex structure of core affect. *Emotion*
21 713 2011;11:705.
- 23
24 714 82 Feldman Barrett L, Russell JA. Independence and bipolarity in the structure of current affect.
25 715 *J Pers Soc Psychol* 1998;74:967.
- 27
28 716 83 Derogatis LR, Unger R. Symptom checklist - 90 - revised, *Corsini encyclopedia of*
29 717 *psychology* 2010.
- 31
32 718 84 Nienhuis FJ, van de Willige G, Rijnders CA, et al. Validity of a short clinical interview for
33 719 psychiatric diagnosis: the mini-SCAN, *Br J Psychiatry* 2010;196:64-8.
- 35
36 720 85 De Jong A, Lubbe PM. Groningse vragenlijst over sociaal gedrag:
37 721 zelfbeoordelingsvragenlijsten voor het vaststellen van problemen in het interpersoonlijke
38 722 functioneren: handleiding: Rob Giel Onderzoekcentrum 2001.
- 40
41 723 86 Diener E, Wirtz D, Tov W, et al. New well-being measures: Short scales to assess flourishing
42 724 and positive and negative feelings, *Soc Indicators Res* 2010;97:143-56.
- 44
45 725 87 Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the
46 726 Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories,
47 727 *Behav Res Ther* 1995;33:335-43.
- 49
50 728 88 Altman EG, Hedeker D, Peterson JL, et al. The Altman self-rating mania scale, *Biol*
51 729 *Psychiatry* 1997;42:948-55.
- 53
54 730 89 van Sonderen E. Sociale Steun Lijst-Interacties (SSL-I) en Sociale Steun Lijst-Discrepanties
55 731 (SSL-D): Noorderlijk Centrum voor Gezondheidsvraagstukken, Groningen 1993.
- 57
58 732 90 Smith BW, Dalen J, Wiggins K, et al. The brief resilience scale: assessing the ability to
59 733 bounce back, *Int J Behav Med* 2008;15:194-200.
- 60

- 1
2
3 734 91 Schreurs P, Van de Willige G. Omgaan met problemen en gebeurtenissen. De Utrechtse
4 735 Coping Lijst (UCL)(Coping with problems and events. The Utrecht Coping List (UCL)), 1998.
5
6
7 736 92 Roenneberg T, Kuehnle T, Juda M, et al. Epidemiology of the human circadian clock, *Sleep*
8 737 *Medicine Reviews* 2007;11:429-38.
9
10 738 93 Rosmalen J, Bos E, De Jonge P. Validation of the Long-term Difficulties Inventory (LDI) and
11 739 the List of Threatening Experiences (LTE) as measures of stress in epidemiological population-
12 740 based cohort studies, *Psychol Med* 2012;42:2599-608.
13
14
15 741 94 Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind, *J Cogn*
16 742 *Neurosci* 1998;10:640-56.
17
18
19 743 95 Armsden GC, Greenberg MT. The inventory of parent and peer attachment: Individual
20 744 differences and their relationship to psychological well-being in adolescence, *Journal of youth*
21 745 *and adolescence* 1987;16:427-54.
22
23
24 746 96 Deković M, Noom MJ, Meeus W. Expectations regarding development during adolescence:
25 747 Parental and adolescent perceptions, *Journal of youth and adolescence* 1997;26:253-72.
26
27 748 97 Brandt PT. Multiple time series models: Sage 2007.
28
29
30 749 98 Opsahl T, Agneessens F, Skvoretz J. Node centrality in weighted networks: Generalizing
31 750 degree and shortest paths, *Social networks* 2010;32:245-51.
32
33 751 99 Epskamp S, Cramer A, Waldorp L, et al. Qgraph: network representations of relationships in
34 752 data, *R package version 0.4* 2011;10.
35
36
37 753 100 Wit E, Abbruzzo A. Factorial graphical lasso for dynamic networks, *arXiv preprint*
38 754 *arXiv:1205.2911* 2012.
39
40 755 101 van Gils A, Burton C, Bos EH, et al. Individual variation in temporal relationships between
41 756 stress and functional somatic symptoms, *J Psychosom Res* 2014;77:34-9.
42
43
44 757 102 Bouwmans ME, Bos EH, Booij SH, et al. Intra-and inter-individual variability of
45 758 longitudinal daytime melatonin secretion patterns in depressed and non-depressed individuals,
46 759 *Chronobiol Int* 2015;32:441-6.
47
48
49 760 103 Honaker J, King G, Blackwell M. Amelia II: A program for missing data, *Journal of*
50 761 *statistical software* 2011;45:Retrieved from <http://www.jstatsoft.org/v45/i07>.
51
52 762 104 Rosmalen JG, Wenting AM, Roest AM, et al. Revealing causal heterogeneity using time
53 763 series analysis of ambulatory assessments: application to the association between depression and
54 764 physical activity after myocardial infarction, *Psychosom Med* 2012;74:377-86.
55
56
57
58
59
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2
3 765 105 Bos EH, Hoenders R, de Jonge P. Wind direction and mental health: a time-series analysis
4 766 of weather influences in a patient with anxiety disorder, *BMJ Case Rep*
5 767 2012;2012:10.1136/bcr.2012-006300.
- 7
8 768 106 Lütkepohl H. New introduction to multiple time series analysis, 2005.
- 9
10 769 107 Snijders TB, Bosker R. R.(1999). Multilevel analysis: An introduction to basic and advanced
11 770 multilevel modeling, .
- 13
14 771 108 Wigman JT, van Os J, Thiery E, et al. Psychiatric diagnosis revisited: towards a system of
15 772 staging and profiling combining nomothetic and idiographic parameters of momentary mental
16 773 states, *PLoS One* 2013;8:e59559.
- 18
19 774 109 Hsu LM. Random sampling, randomization, and equivalence of contrasted groups in
20 775 psychotherapy outcome research. *J Consult Clin Psychol* 1989;57:131.

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23 777 **Authors' contributions**

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26 778 JTWW conceived the study. JTWW and SHB designed and are executing the study and drafted
27
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29 779 the first versions of the manuscript. LW, PdJ, JvO, MCW helped conceptualize the study and
30
31 780 provided overall supervision, SS contributed to the study design, specifically to the data
32
33 781 gathering and data management part. All authors critically reviewed the manuscript, and
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35 782 collaborated in the discussion of the intellectual content of the manuscript. All authors read and
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37 783 approved the final manuscript.

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51 790 the preparation of the manuscript.

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3 792 **Competing interests**
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6 793 The authors declare that they have no competing interests.
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796 **Tables**

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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	T1	T1	T1	T2	T3
							(3m)			(3m)		
<i>Demo-graphics</i>	Gen. Health	SR	Demogr, conf.	5	X				X [†]			
	Vignette	INT	History psychosis	5	X**							
<i>Psychosis</i>	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* [†]
<i>Psychopathology</i>	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		

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Table 1. Continued.

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
<i>Social functioning</i>	GVSG-45	SR	Social functioning	8		X		X			X	X
	Flourishing Sc	SR	Well-being	1		X		X			X	X
<i>Risk & resilience</i>	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***		

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

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3 800 * Only administered when PQ score is 6 or higher.
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6 801 ** Only administered when there is a history of a psychiatric disorder according to the information on the General Health
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9 802 Questionnaire
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12 803 *** Offered to participants as optional.
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15 804 † Available as ROM data for all individuals in clinical care for mental health at each measurement wave.
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18 805 ‡ Send out several weeks before the daily diary period to screen on exclusion criteria
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22 806 # Administered only to subgroup 4
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3 808 **Figure titles and legends**
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10 810 Figure 1. Parameters of symptom networks.
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22 814 Note. Light grey area within blue dashed square indicates optional measurements.
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32 817 Figure 3. Definition of subgroups.
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3 819 **Additional files**
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13 822 Title: Table S1. Diary items
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16 823 Description: Original Dutch diary items and their translation to English
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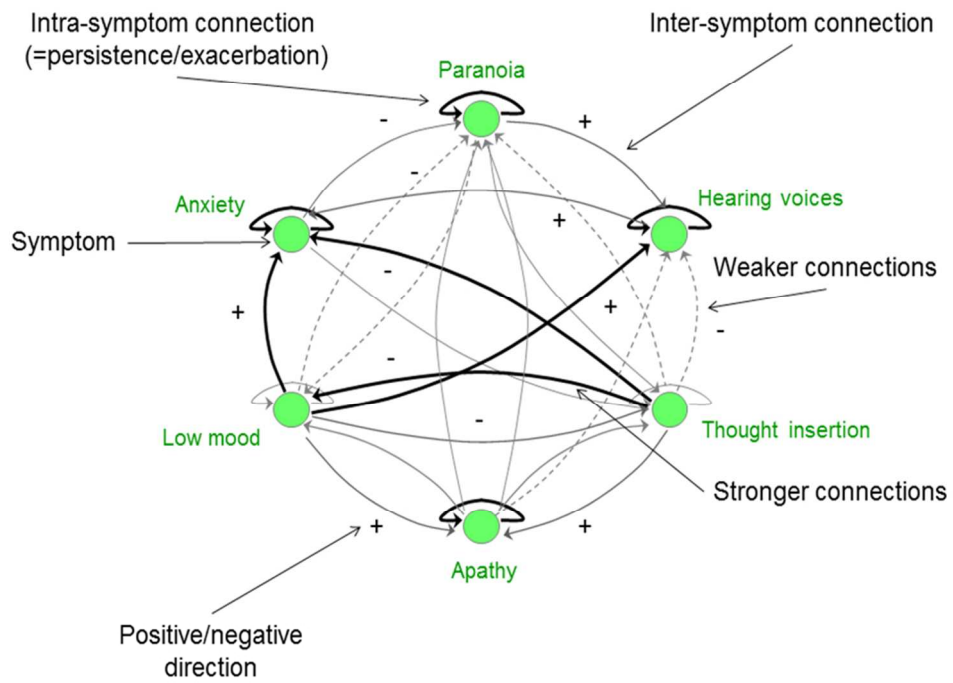
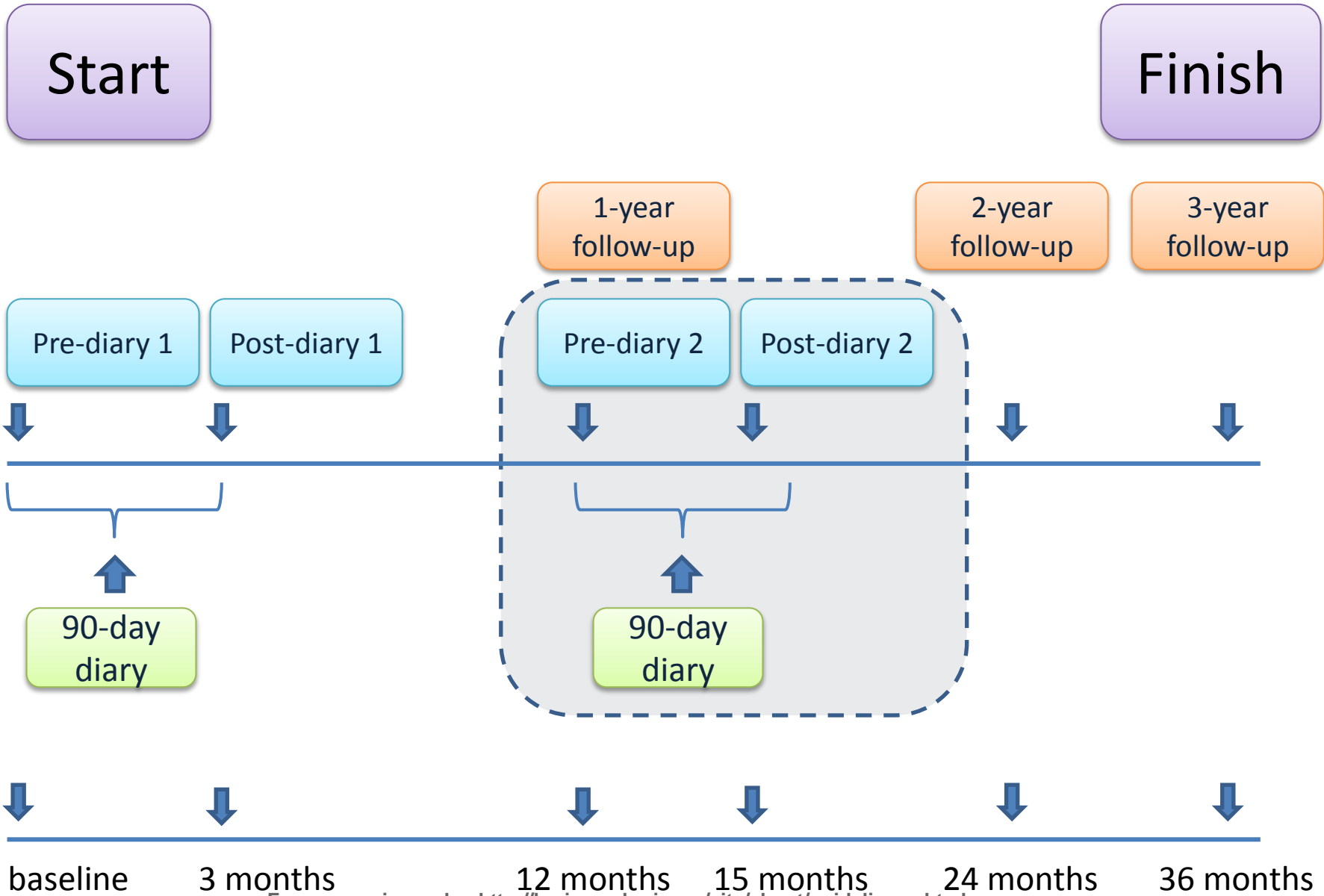


Figure 1. Parameters of symptom networks.

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General population

Clinical population

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N=100 from the general population (18-35 year) completed the CAPE

N=25 with highest scores invited for diary study

Subgroup 1

Score on PQ-16 below 6: no follow-up

Subgroup 2

CAARMS interview: no Ultra High Risk

Subgroup 3

All new patients in mental health care age 18-35 years completed the PQ-16

Score on PQ-16 of 6 or higher: follow-up with CAARMS interview

CAARMS interview: Ultra High Risk

Subgroup 4

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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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

1		geslapen?				
2						
3						
4	10	Hoeveel uur heb je	About how many	Hours, minutes	0 - 24	Sleep
5		afgelopen nacht	hours did you sleep			
6		ongeveer geslapen?	tonight?			
7						
8	11	Heb je vandaag	Did you sleep during	• No (skip to 13)	0 - 1	Sleep
9		overdag geslapen?	the day today (naps)?	• Yes		
10		(dutjes)				
11	12	Hoe lang in totaal?	How long in total did	Hours, minutes	0 - 12	Sleep
12			you sleep during the			
13			day today?			
14						
15	<i>Instruction</i>	<i>Alle items gaan</i>	<i>From now on, all</i>			
16		<i>vanaf nu over de</i>	<i>items involve the past</i>			
17		<i>afgelopen dag (denk</i>	<i>day (think about how</i>			
18		<i>aan hoe je je</i>	<i>you felt on average</i>			
19		<i>vandaag gemiddeld</i>	<i>today)</i>			
20		<i>voelde)</i>				
21						
22	13	Ik voelde me	I felt relaxed today	Not at all – Very much	0 – 100	Positive
23		vandaag ontspannen				deactivation
24	14	Ik voelde me	I felt calm today	Not at all – Very much	0 – 100	Positive
25		vandaag kalm				deactivation
26	15	Ik voelde me	I felt satisfied today	Not at all – Very much	0 – 100	Positive
27		vandaag tevreden				deactivation
28	16	Ik voelde me	I felt energetic today	Not at all – Very much	0 – 100	Positive
29		vandaag energiek				activation
30	17	Ik voelde me	I felt enthusiastic	Not at all – Very much	0 – 100	Positive
31		vandaag enthousiast	today			activation
32	18	Ik voelde me	I felt cheerful today	Not at all – Very much	0 – 100	Positive
33		vandaag opgewekt				activation
34	19	Ik voelde me	I felt apathetic today	Not at all – Very much	0 – 100	Negative
35		vandaag lusteloos				deactivation
36	20	Ik voelde me	I felt tired today	Not at all – Very much	0 – 100	Negative
37		vandaag moe				deactivation
38	21	Ik voelde me	I felt down today	Not at all – Very much	0 – 100	Negative
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	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

1						
2						
3	35	Ik vond mijn leven	I found my life was	Not at all – Very much	0 – 100	Worthlessness
4		vandaag de moeite	worthwhile today			
5		waard				
6						
7	36	Ik had vandaag last	I was bothered by	Not at all – Very much	0 – 100	Physical
8		van lichamelijke	physical symptoms			discomfort
9		klachten	today			
10	37	Ik had vandaag de	Today I had the	Not at all – Very much	0 – 100	Disorganized
11		neiging iets	tendency to do			thoughts
12		onbeheersts te doen	something			
13			unrestrained/wild			
14						
15	38	Mijn gedachten	My thoughts wouldn't	Not at all – Very much	0 – 100	Disorganized
16		lieten me vandaag	leave me alone today			thoughts
17		niet los				
18	39	Mijn gedachten	My thoughts were	Not at all – Very much	0 – 100	Disorganized
19		waren vandaag	racing today			thoughts
20		versneld				
21						
22	40	Mijn gedachten	My thoughts were	Not at all – Very much	0 – 100	Disorganized
23		waren vandaag	difficult to express			thoughts
24		moeilijk te uiten	today			
25						
26	41	Er is vandaag iets	Today something	Not at all – Very much	1 – 7	Strange
27		vreemds met mij of	strange happened to			impressions /
28		om mij heen	me or around me that			Delusions
29		gebeurd dat ik	was difficult for me to			
30		moeilijk kon	explain			
31		verklaren				
32						
33	42	Ik hoorde vandaag	Today I heard voices	Not at all – Very much	1 – 7	Hallucinations
34		stemmen die	that others couldn't			
35		anderen niet	hear			
36		hoorden				
37	43	Ik zag vandaag	Today I saw things	Not at all – Very much	1 – 7	Hallucinations
38		dingen die anderen	that others couldn't			
39		niet zagen	see			
40						
41	44	Ik had vandaag het	Today I had the	Not at all – Very much	0 – 100	Paranoia
42						
43						
44						
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3					
4		gevoel dat anderen	feeling that others did		
5		me niet mochten	not like me		
6	45	Ik had vandaag het	I felt that others could	Not at all – Very much	0 – 100 Delusions
7		gevoel dat anderen	read my thoughts		
8		mijn gedachten	today		
9		konden lezen			
10	46	Ik voelde me	I felt unreal today	Not at all – Very much	0 – 100 Delusions
11		vandaag			
12		onwerkelijk			
13	47	Ik had vandaag het	I felt that others could	Not at all – Very much	0 – 100 Delusions
14		gevoel dat anderen	control me today		
15		controle over me			
16		uitoefenden			
17	48	Ik kon vandaag	I could experience	Not at all – Very much	0 – 100 Flat affect
18		plezier ervaren	pleasure when nice		/anhedonia
19		wanneer er leuke	things happened today		
20		dingen gebeurden			
21	49	Er kwam vandaag	I did not get many	Not at all – Very much	0 – 100 Motivation /
22		weinig uit mijn	things done today		drive
23		handen			
24	50	Ik had vandaag zin	I felt like undertaking	Not at all – Very much	0 – 100 Motivation /
25		om dingen te	something to day		drive
26		ondernemen			
27	51	Ik deed dingen ‘op	I did things on	Not at all – Very much	0 – 100 Mindfulness
28		de automatische	automatic without		
29		piloot’, zonder mij	being conscious of		
30		erg bewust te zijn	what I was doing		
31		van wat ik aan het	today		
32		doen was			
33	52	Mijn eetlust was	My appetite today was	Smaller than normal – Larger than normal	0 – 100 Appetite
34		vandaag			
35	53	Hoe gestrest was je	How stressed were	Not at all – Very much	0 – 100 Stress
36		vandaag?	you today?		
37					
38					
39					
40					
41					
42					
43					
44					
45					
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47					
48					
49					

1					
2					
3	54	In welke mate zijn	To what extent did	Not at all – Very much	0 – 100 Positive events
4		er vandaag positieve	positive events happen		
5		gebeurtenissen	today?		
6		geweest?			
7					
8	<i>Instruction</i>	<i>Denk aan de</i>	<i>Think about the most</i>		
9		<i>belangrijkste</i>	<i>important positive</i>		
10		<i>positieve</i>	<i>event of today</i>		
11		<i>gebeurtenis van de</i>			
12		<i>afgelopen dag</i>			
13					
14	55	Hoe plezierig was	How pleasant was this	Neutral – Very pleasant	0 – 100 Positive events
15		deze gebeurtenis?	event?		
16	56	Hoe belangrijk was	How important was	Very unimportant – Very important	0 – 100 Positive events
17		deze gebeurtenis	this positive event to		
18		voor mij?	me?		
19					
20	57	Was deze positieve	Was this positive	• No (skip to 59)	0 - 1 Positive events
21		gebeurtenis	event planned?	• Yes	
22		gepland?			
23					
24	58	Ik keek er naar uit	I was looking forward	Not at all – Very much	0 – 100 Positive events
25			to it		
26	59	In welke mate zijn	To what extent did	Not at all – Very much	0 – 100 Negative events
27		er vandaag	negative events		
28		negatieve	happen today?		
29		gebeurtenissen			
30		geweest?			
31					
32	<i>Instruction</i>	<i>Denk aan de</i>	<i>Think about the most</i>		
33		<i>belangrijkste</i>	<i>important negative</i>		
34		<i>negatieve</i>	<i>event of today</i>		
35		<i>gebeurtenis van de</i>			
36		<i>afgelopen dag</i>			
37					
38	60	Hoe onplezierig was	How unpleasant was	Very unpleasant - Neutral	0 – 100 Negative events
39		deze gebeurtenis?	this event?		
40	61	Hoe belangrijk was	How important was	Very unimportant – Very important	0 – 100 Negative events
41		deze gebeurtenis	this negative event to		
42					
43					
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3						
4	62	voor mij? Was deze negatieve gebeurtenis gepland?	me? Was this negative event planned?	<ul style="list-style-type: none"> • No (skip to 59) • Yes 	0 - 1	Negative events
5						
6						
7						
8						
9	63	Ik zag er tegen op	I dreaded it	Not at all – Very much	0 – 100	Negative events
10						
11	64	Welke gebeurtenis was het meest spannend of stressvol?	Which event was most exciting or stressful?	<ul style="list-style-type: none"> • The negative event • The positive event 	1 - 2	Event stressfulness
12						
13						
14						
15	65	Hoe stressvol of spannend was deze gebeurtenis?	How stressful or exciting was this event?	Not at all – Very much	0 – 100	Event stressfulness
16						
17						
18						
19	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	<ul style="list-style-type: none"> • 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
20						
21						
22						
23						
24						
25						
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34						
35	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
36						
37						
38						
39						
40	68	Ik was liever wat meer in gezelschap	I would have preferred more company	Not at all – Very much	0 – 100	Social context
41						
42						
43						
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49						

1		geweest				
2						
3						
4		Ik vond het	I found today's	Very unpleasant – Very pleasant	0 – 100	Social context
5	69	gezelschap van	company mostly			
6		vandaag				
7		overwegend				
8						
9	70	Voelde je je	Did you feel supported	Not at all – Very much	0 – 100	Social context
10		vandaag gesteund?	today?			
11	71	Ik had liever meer	I would have liked to	Not at all – Very much	0 – 100	Social context
12		steun gevoeld	feel more support			
13	72	Heb je vandaag met	Have you had a	<ul style="list-style-type: none"> • No (skip to 78) • Yes 	0 – 1	Social context
14		iemand een gesprek	conversation with			
15		gevoerd?	someone today?			
16	<i>Instruction</i>	<i>Denk aan het voor</i>	<i>Think about the most</i>			
17		<i>jou belangrijkste</i>	<i>important</i>			
18		<i>gesprek van</i>	<i>conversation of today</i>			
19		<i>vandaag (mag ook</i>				
20		<i>via telefoon of</i>				
21		<i>mobiele</i>				
22		<i>berichtenapp)</i>				
23	73	Met wie was dit	With whom was this	<ul style="list-style-type: none"> • Family (except partner) <ul style="list-style-type: none"> ○ Father ○ Mother ○ Other • Partner • Friend • Other 	1 - 7	Social context
24		gesprek?	conversation?			
25						
26						
27						
28						
29						
30						
31						
32						
33						
34						
35	74	Hoe kritisch was	How critical was this	Not at all – Very much	0 – 100	Expressed
36		deze persoon naar	person towards you?			emotions
37		jou toe?				
38	75	Hoe warm was deze	How warm was this	Not at all – Very much	0 – 100	Expressed
39		persoon naar jou	person towards you?			emotions
40		toe?				
41	76	In welke mate	To what extent did this	Not at all – Very much	0 – 100	Expressed
42						
43						
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49						

	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	<ul style="list-style-type: none"> • 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
<i>Instruction</i>	<i>Het volgende item gaat over morgen</i>	<i>The next item is about tomorrow</i>			
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



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Manuscripts

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2
3 1 **Title: A study protocol for a prospective cohort study examining the predictive potential of**
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6 2 **dynamic symptom networks for the onset and progression of psychosis: The Mapping**
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8 3 **Individual Routes of Risk and Resilience (Mirror) study**

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3 35 **Abstract** (295 words)
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8 37 Introduction: Our current ability to predict the course and outcome of early psychotic symptoms
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10 38 is limited, hampering timely treatment. To improve our understanding of the development of
11
12 39 psychosis, a different approach to psychopathology may be productive. We propose to re-
13
14 40 conceptualize psychopathology from a network perspective, according to which symptoms act as
15
16 41 a dynamic, interconnected system, impacting on each other over time and across diagnostic
17
18 42 boundaries to form symptom networks. Adopting this network approach, the Mapping Individual
19
20 43 Routes of Risk and Resilience (Mirorr) study aims to determine whether characteristics of
21
22 44 symptom networks can predict illness course and outcome of early psychotic symptoms.
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29 46 Methods and analysis: The sample consists of N=100 participants aged 18-35 years, divided into
30
31 47 four subgroups (N=4x25) with increasing levels of severity of psychopathology, representing
32
33 48 successive stages of clinical progression. Individuals representing the initial stage have a
34
35 49 relatively low expression of psychotic experiences (general population), whereas individuals
36
37 50 representing the end stage are help-seeking and display a psychometric expression of psychosis,
38
39 51 putting them at ultra-high risk for transition to psychotic disorder. At baseline and 1-year follow-
40
41 52 up, participants report their symptoms, affective states and experiences for three consecutive
42
43 53 months in short, daily questionnaires on their smartphone, which will be used to map individual
44
45 54 networks. Network parameters, including the strength and directionality of symptom connections
46
47 55 and centrality indices, will be estimated, and associated to individual differences in and within-
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49 56 individual progression through stages of clinical severity and functioning over the next three
50
51 57 years.
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6 59 Ethics and dissemination: The study has been approved by the local medical ethical committee
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8 60 (ABR no. NL52974.042.15). The results of the study will be published in (inter)national peer-
9
10 61 reviewed journals, presented at research, clinical and general public conferences. The results will
11
12 62 assist in improving and fine-tuning dynamic models of psychopathology, stimulating both
13
14 63 clinical and scientific progress.
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18 64

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20 65 Trial registration:

21
22 66 Netherlands Trial Register NTR6205, Registered 27 October 2016.

23
24 67 <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6205>
25
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27 68

28
29 69 Strengths and limitations of this study:

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31
32 70 • One of the first studies examining the predictive potential of dynamic symptoms
33
34 71 networks for the onset and progression of psychopathology
35
36 72 • The study design allows considering within- and between-individual variation in
37
38 73 symptomatology, both at the micro (day) and macro (year) level
39
40 74 • A dynamic, transdiagnostic approach is adopted; outcome measures include clinical
41
42 75 stage, diagnosis, symptoms of a broad range of disorders and functioning
43
44 76 • With three yearly follow-ups, we may not capture all transitions to psychosis
45
46 77 • The exploratory nature of the study warrants replication of the findings
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81 Words (main text): 5035

For peer review only

82 Introduction

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

89
90 Current diagnostic systems in psychiatry are challenged by issues such as high levels of
91 comorbidity, clinical heterogeneity, non-specific treatment effects, and lack of diagnosis-specific
92 biological/ cognitive markers [8-12]. Despite this, traditional diagnoses still dominate psychiatric
93 research, hampering scientific progress. These diagnoses are based on clinical presentation of
94 adults with long-established illness [13], and classify individuals according to distinct diagnostic
95 labels [8] (e.g. schizophrenia or major depressive disorder). However, it is increasingly
96 acknowledged that psychopathology is expressed dimensionally, representing a quantitative as
97 well as qualitative deviations from mental health [8, 14-19]. In addition, it is increasingly
98 accepted that mental disorders do not emerge fully formed in adulthood but evolve gradually,
99 often manifesting for the first time already in adolescence [20, 21].

100
101 A model that was designed to capture this continuity of both severity and time is the clinical
102 staging model [22, 23]. This model describes psychopathology as ranging, through subsequent
103 but qualitatively different stages, from increased risk of mental illness at the lowest level through
104 progressive stages of severity, resulting in separable but overlapping syndromes at the highest

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2
3 105 levels [24, 25]. Stage 0 represents individuals at increased risk without symptoms; Stage 1a
4
5 106 represents ‘help-seeking’ individuals with mild, non-specific symptoms; Stage 1b represents
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7
8 107 individuals with an ‘attenuated syndrome’, with moderate but subthreshold symptoms and
9
10 108 moderate functional decline; Stage 2 holds individuals with a first episode of a clinical,
11
12 109 ‘discrete’, disorder; Stage 3 holds individuals with persistent or recurrent illness [13, 22, 23] and
13
14 110 Stage 4 represents individuals with chronic illness. This clinical staging model further
15
16
17 111 hypothesizes that psychopathological expression is more multi-dimensional, non-specific and
18
19
20 112 more susceptible to intervention in early stages and becomes more crystallized, disorder specific
21
22 113 and treatment-resistant in later stages [25]. This model offers a theoretical representation that
23
24 114 seems to fit better to the true nature and development of psychopathology [9-11, 26], and hence
25
26
27 115 may improve diagnostic accuracy. It has been developed most extensively in the context of
28
29 116 psychosis [23, 25, 27], but needs further empirical validation. Longitudinal studies assessing
30
31 117 predictive validity of the model have mostly concentrated around the transition from stage 1b
32
33 118 (ultra-high risk) to stage 2 (first psychotic episode), and found 3-year transition rates of 36%
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35
36 119 [28]. In addition, some biological and cognitive measures seem to be more abnormal in more
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38
39 120 severe stages, and these measures seem to change in patients who progress in stage [29, 30].
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41 121 Finally, some treatments seem more effective for individuals in early stages [30]. Taken together,
42
43 122 these studies provide at least some support for the clinical staging model of psychosis. However,
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45
46 123 many questions still remain, e.g. about what drives progression through subsequent stages and
47
48 124 how the thresholds between the stages should be defined exactly.

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53 126 The expression and development of early psychotic symptoms are highly variable [31-34] and
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55 127 difficult to predict [28, 35]. One reason for this is that many studies so far have focused on early
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3 128 psychotic symptoms as specific predictors of later schizophrenia. However, this approach may be
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5
6 129 too narrow [25, 33, 36] because early psychotic symptoms are often transitory [37-39], also
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8 130 occur in the context of [6, 7, 40-42] and predict other mental disorders [28, 37, 43, 44], and vice
9
10 131 versa [45-47]. High levels of comorbidity [48] and overlap of risk factors [49-52] also challenge
11
12 132 the assumed independence of psychosis from other symptom domains. In addition, the
13
14 133 information that is used to predict course and outcome is often based on cross-sectional
15
16
17 134 assessment of symptoms and comparisons are often made at the group level. However,
18
19
20 135 symptoms can vary substantially over time, both over short (i.e. days) and long intervals
21
22 136 (months, years), within one individual, and can also cross diagnostic borders [53]. This means
23
24 137 that the clinical picture can change, particularly in the early phase of a disorder [25]. These
25
26
27 138 characteristics of psychopathology suggest that the 'static' model prediction may not be fit for
28
29 139 the purpose. This is reflected in the modest accuracy and replicability of static prediction models
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31
32 140 in the psychosis prediction field [54-56].
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36 142 The above-mentioned challenges may be overcome by taking a different approach towards the
37
38 143 conceptualization of psychopathology, its measurement and the way we model it. By taking a
39
40 144 more transdiagnostic approach, incorporating symptoms and experiences from multiple
41
42
43 145 (psychotic and non-psychotic) domains, the narrow focus on the sole dimension of psychosis can
44
45
46 146 be broadened. Furthermore, by modelling individual patterns of symptom patterns over time, a
47
48 147 more developmental as well as a more personalized approach can be taken that, in addition,
49
50 148 builds on a more detailed inventory of symptomatology compared to baseline (cross-sectional)
51
52 149 assessment scores. Finally, modelling the interconnectivity between symptoms by mapping
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55 150 individual symptom networks and patterns of co-occurrence in and over time could provide us
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3 151 with a better idea of how psychopathology develops and may give us clues on what processes
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6 152 may drive progression through subsequent clinical stages [57, 58].
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10 154 *A network approach to psychopathology*

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12 155 A focus on dynamic symptom networks requires an innovative approach to psychopathology.

13 156 One of the currently promising alternative approaches comes from network theory. From this

14
15 157 network perspective, psychopathology, at a phenomenological level, is hypothesized to result

16
17 158 from interactions between symptoms [11, 59, 60]. Mental disorders are thus represented by sets

18
19 159 of symptoms, connected in networks by causal relations [11, 59] (see also Figure 1). These

20
21 160 networks are dynamic and capture reciprocal influences between symptoms over time (e.g.,

22
23 161 feedback loops). Importantly, symptoms are acknowledged as causal factors in

24
25 162 psychopathological development: one symptom (e.g., anxiety) can cause another (e.g., paranoia).

26
27 163 This is in sharp contrast with current dominant models that represent symptoms as independent

28
29 164 indicators of underlying, latent constructs (e.g., schizophrenia). As stress is important in the

30
31 165 development of psychosis [61, 62], the sensitivity of symptom networks to risk-enhancing

32
33 166 (trauma) and risk-reducing (coping, social support) factors [63, 64] also needs attention. The

34
35 167 network approach has been successfully applied in other fields [65, 66], but is relatively novel in

36
37 168 psychiatry, where it has been investigated mainly in common mental disorders [67], but not

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39 169 psychosis.
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43 171 *Aims and hypotheses*

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45 172 With the Mapping Individual Routes of Risk and Resilience (Mirrr) study, we aim to

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47 173 investigate the hypothesis of dynamic symptom networks as the basis of psychopathology in
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3 174 general and psychosis in particular. The key hypothesis to be tested centres on the question
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6 175 whether individual networks of a broad scope of transdiagnostic symptoms can predict course
7
8 176 and outcome of early psychopathology in young individuals at increased risk for psychosis and
9
10 177 other severe mental illness. Furthermore, we aim to investigate the additional hypothesis of
11
12 178 symptom networks as markers/indicators of progression of illness through successive clinical
13
14
15 179 stages. Taking a broader, multidimensional and process-oriented approach, we will examine how
16
17 180 symptoms of multiple domains influence each other over time and across diagnostic boundaries,
18
19
20 181 in interaction with environmental factors. More specifically, we hypothesize that different
21
22 182 clinical stages will be characterized by different symptom networks. In addition, we expect that
23
24 183 characteristics of these networks can predict progression through clinical stages. We will explore
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26
27 184 the predictive potential of several characteristics, such as the strength and directionality of
28
29 185 symptom connections (see Figure 1) and centrality indices (information about the position of a
30
31 186 symptom in the network). Finally, we will evaluate the predictive potential of these
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33
34 187 characteristics against (more) static assessments of symptom severity.
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39 189 The Mirorr study is unique in its design and in its attempt to (i) bring together a network
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41 190 approach to psychopathology and the clinical staging model, (ii) take a broader perspective on
42
43 191 mental illness by (a) taking a transdiagnostic approach towards symptomatology and (b) defining
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45
46 192 outcome in more broadly in the context of clinical staging (incorporating both clinical and
47
48 193 functional outcomes), and (iii) modelling individual symptom networks over time by using time-
49
50 194 series data, enabling us to model more personalized pathways of psychopathological
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53 195 development.
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199 *Outcome measures*

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

208

209 Please insert Figure 1 here.

210

211 Methods and analysis*212 Study design*

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

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3 220 functioning and stress. These diary data are used to map individual symptom networks. For the
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5
6 221 second diary period, participants can also opt to keep continuing the questionnaire follow-ups,
7
8 222 but not have a second diary period. A flowchart of the study is presented in Figure 2.
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13 224 Please insert Figure 2 here.

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17 226 *Study population*

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19
20 227 The total sample comprises of 175 individuals of 18-35 years, whereof 100 will enter the main
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22 228 study (i.e. the daily diary study and the yearly follow-ups). For the main study, there will be four
23
24 229 subsamples, all n=25 (Figure 3) with each subgroup having an increasingly more severe
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26
27 230 psychopathological level and thus representing subsequent clinical stages. For subsample 1
28
29 231 (lowest level of psychopathology and thus lowest clinical stage), 100 individuals will be
30
31 232 randomly selected from the general population in the North of the Netherlands and administered
32
33 233 the Community Assessment of Psychic Experiences (CAPE) [72]. Of all the respondents who
34
35
36 234 meet the inclusion and exclusion criteria of the study, the highest scoring quartile will be
37
38
39 235 included in the main study. For subsamples 2-4, individuals will be recruited from mental health
40
41 236 care institutions in the four Northern provinces in The Netherlands. For all individuals who are
42
43 237 referred to mental health care, psychotic symptoms are routinely screened by means of, among
44
45
46 238 other things, the Prodromal Questionnaire (PQ) [73]. If the score on the PQ is 6 or higher, the
47
48 239 Comprehensive Assessment of At Risk Mental State (CAARMS) [74] is administered as well.
49
50 240 With these scores it is determined for which subsample (2-4, explained below) eligible subjects
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53 241 will be recruited, where a higher subsample indicates higher levels of psychopathology.
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3 243 Please insert Figure 3 here.
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8 245 In order to be eligible to participate in the study, subjects must meet all of the following criteria:
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10 246 1) age between 18 and 35 years, 2) read and speak Dutch fluently, 3) capable of following the
11

12 247 research procedures, 4) provide Informed Consent. In addition, participants of subsample 1
13

14 248 should *not* be in clinical care for mental health at the moment of screening. In contrast,
15

16 249 participants of subsample 2-4 *should* currently be in clinical care for mental health. In addition,
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18 250 participants of subsample 2 should have mild, non-psychotic psychopathology, as evidenced by a
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20 251 score below 6 on the PQ, participants of subsample 3 should have mild psychopathology
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22 252 including subclinical psychotic symptoms, as evidenced by a score of or above 6 on the PQ, but
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24 253 are not at ultra-high risk (UHR) for psychosis, as indexed by the CAARMS. Finally, participants
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26 254 of subsample 4 should be at UHR for psychosis, as indexed by the CAARMS. Exclusions criteria
27

28 255 are: 1) a history of or current psychotic episode, according to the Diagnostic and Statistical
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30 256 manual of Mental Disorders-IV (DSM-IV) criteria; 2) significant hearing or visual problems
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32 257 impairments; 3) pregnancy, as stated on a general health questionnaire.
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41 259 *Procedure*
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43 260 Recruitment
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46 261 To recruit subsample 1, the study will be announced at several university sites, public places in
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48 262 Groningen, and social media (start recruitment: September 2015). Interested individuals can
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50 263 contact the researchers by phone or e-mail for more information. They will then be sent an
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52 264 information letter, flyer, informed consent form and the initial screenings questionnaires. After
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54 265 receiving the completed screening questionnaires and informed consent forms, the 25 (out of
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3 266 100) individuals with the highest CAPE scores will be invited to participate in the main study
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6 267 (first inclusion: December 2015). For subsample 2-4, individuals will be recruited from mental
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8 268 health care institutions in four northern Dutch provinces (first inclusion: April 2016). To which
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10 269 subsample they will be recruited is determined using the instruments described under study
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12 270 population. For these sites where patients give their consent for receiving information about
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14 271 ongoing research projects, a package containing detailed information on the study (information
15
16 272 letter and flyer), along with screening questionnaires and an informed consent form will be sent
17
18 273 to potential participants. Interested individuals can fill out and return requested forms (including
19
20 274 informed consent form). After receiving the requested forms, an individual's therapist will be
21
22 275 consulted about several exclusion criteria. For these sites where participants do not give consent
23
24 276 in advance, the individual's clinical worker will be provided a package containing detailed
25
26 277 information on the study (information letter and flyer), along with screening questionnaires and
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28 278 an informed consent form. The clinical worker will pre-screen his/her client on the exclusion
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30 279 criteria of the study and hand over the package if he/she fits the profile of the study. Study
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32 280 participants can continue their therapy and medical treatment as usual; they will be asked to
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34 281 register any changes in medication or treatment during the daily ambulatory assessments.
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43 283 Screening

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45 284 The information package that interested individuals receive contains an information letter, two
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47 285 screening questionnaires and an informed consent form. All potential participants can ask
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49 286 questions before completing informed consent form or the screening questionnaires. As
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51 287 mentioned in the information letter, in case subjects should decide to participate, they should fill
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53 288 out and send back these questionnaires and the informed consent form. This consent form covers
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3 289 the baseline ambulatory assessment period and the yearly follow-up assessments (three in total).
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5 290 On this consent form permission will be asked to re-invite subjects for the follow-up ambulatory
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8 291 assessment period, for which they have to complete a separate consent form (one year later).
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10 292 Also, permission will be asked to use data from the psychiatric case register of the North of the
11
12 293 Netherlands. The first screening questionnaire is a screening questionnaire on general health,
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14 294 containing questions on demographics, health complaints (such as visual or hearing
15
16 295 impairments), pregnancy, drug and alcohol use, medication use, and mental health problems.
17
18 296 This will be used to screen on exclusion criteria. The second screening questionnaire is the
19
20 297 CAPE. This instrument is used to screen individuals recruited from the general population
21
22 298 (subsample 1) on psychotic experiences but will be administered to all participants to enable
23
24 299 group comparisons on the level of subclinical psychotic experiences. The highest scoring quartile
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26 300 (n=25) will subsequently be included in the main study. Subjects will have one week to decide
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28 301 about participation.
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36 303 Baseline interview and ambulatory assessments (year one)
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38 304 If subjects are eligible to enter the study and agree to participate, they will be invited (by
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40 305 telephone or e-mail) for an introduction interview at the University Medical Centre Groningen. A
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42 306 few days before the interview, self-report questionnaires will be administered via email (see data
43
44 307 management for more information). The questionnaires assess symptomatology, functioning,
45
46 308 clinical stage, and factors of risk and resilience. During the interview, the study will be explained
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48 309 to them in detail and a diagnostic psychiatric interview will be held. If in an exceptional case the
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50 310 participant does not possess a smartphone, this will be provided to the participant during the
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52 311 study period. An appointment for an end-of-study interview will be planned. Also, the
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3 312 participants will be asked to designate suitable moments at which the researcher can call him/her
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6 313 to inquire on the progression of the study and to help with any problems the participant may
7
8 314 experience.

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12 316 The participants then start completing the electronic daily diary for three months. Every evening,
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15 317 they receive a text message with a link which directs them to a web-based diary questionnaire in
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17 318 a secure environment. Measurements are always in the evening, asking about the past day; exact
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19 319 times can vary per person (but not per day) and are fixed according to the participant's wishes.
20
21 320 However, *all* participants have 24 hours between each measurement point. For example,
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23 321 participant A will always receive her text message at 22.00 and participant B always at 21.15. A
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25 322 window of one and a half hour will be allowed to fill in the diary, and reminder messages will be
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27 323 send every half hour. Short questions will be presented on sequential screens, which are mainly
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29 324 answered using visual analogue scales. During the research period, participants are also provided
30
31 325 a paper log, in which they can note any unusual events, start of or changes in medication use and
32
33 326 problems they encounter with the research procedures. The researchers will telephone the
34
35 327 participants six times during the study period (every other week), to motivate the participant,
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37 328 answer questions about the study procedures and provide technical help. They will also be
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39 329 available by telephone and e-mail if participants need help at other moments.
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48 331 During the end-of-ambulatory-assessment (3 months after baseline) interview participants will
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50 332 fill out an online questionnaire battery once more, and report on any changes in medical
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52 333 treatment. Furthermore, they will also be asked to comment on the data collection and the study
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54
55 334 in general. We will use this information to check whether the study affected their thoughts and
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3 335 behaviours in any way, whether there had been special events that might have affected the data
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6 336 collected.

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10 338 Follow-up assessments

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12 339 One, two and three years after baseline, all participants will receive questionnaires about

13 340 functioning and clinical stage via email. The participants will be able to fill these in at home.

14
15 341 Shortly after filling in the questionnaires, participants will be interviewed by telephone or face-

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17 342 to-face at one of our research facilities, depending on their preferences, to establish the

18
19 343 presence/absence of psychiatric disorders with a diagnostic interview. In addition, to distinguish

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21 344 individuals in clinical stage 1a from individuals in clinical stage 1b (all individuals with a score

22
23 345 of 6 or higher on the PQ-16), data from the CAARMS interview is needed. Participants will be

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25 346 reminded about the follow-up assessments a few weeks before the actual follow-up by means of

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27 347 an information letter.

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31 349 Follow-up ambulatory assessment period (year two)

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33 350 In the aforementioned information letter, participants will also read information about a second

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35 351 ambulatory assessment period that they can enrol in. If they are interested, they are invited for

36
37 352 another introduction interview (given that they still fulfil the in- and exclusion criteria as

38
39 353 evidenced by their answers to an online version of a general health questionnaire). This interview

40
41 354 is similar to the introduction interview at baseline (i.e., questionnaire battery and procedures). An

42
43 355 exception is that questionnaires about symptomatology, functioning and clinical stage will not be

44
45 356 administered, because they have been covered already by the usual follow-up assessments.

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47 357 Participants then start their second three-month period of ambulatory assessments one year after

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3 358 the first diary period. The end-of-ambulatory-assessment interview will take place, again with
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6 359 similar questionnaires to the one held at baseline.
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10 361 *Instruments*

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12 362 A complete overview of the instruments used throughout the study is presented in Table 1.
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17 364 Please insert Table 1 here.
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21
22 366 *Diary measures*

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24 367 The items assessed in the daily questionnaires will be used to model individual networks of
25
26
27 368 symptoms, experiences and emotions. Items included in the dairy questionnaires were chosen
28
29 369 from a transdiagnostic perspective and cover a broad range of feelings and experiences that are
30
31 370 characteristic for (subclinical) psychotic experiences, depression, anxiety, mania, obsessive
32
33 371 compulsive behaviour and anger. These disorders are known for the co-occurrence of psychotic
34
35 372 symptoms [6, 7] and comorbidity [48]. For the complete item list, see Additional file 1, Table
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37 373 S1.
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43 375 Positive psychotic experiences can be divided into five categories, namely paranoia, delusions,
44
45 376 hallucinations, megalomania, and paranormal beliefs [75]. Because paranormal beliefs are often
46
47 377 stable over time, we will include items covering the first four categories. Negative symptoms of
48
49 378 psychosis will be covered by items about flattened affect (e.g., anhedonia, low motivation, social
50
51 379 withdrawal), which resemble closely the negative symptoms of the CAPE. Most items are
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53 380 adopted from previous ESM studies [76-78], and all items are adapted for daily use.
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6 382 Symptoms of depression will be measured using items that correspond closely to the patient
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8 383 health questionnaire (PHQ-9) [79], a self-administered questionnaire for screening and
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10 384 measuring the severity of depression. Anxiety symptoms will be measured using items that
11
12 385 correspond closely to the Hospital Anxiety and Depression Scales – Anxiety (HADS-A) [80].
13
14
15 386 Mania, obsessive compulsive behaviour and anger are measured with items that correspond
16
17 387 closely to items from the DSM-V – screener for the corresponding clinical disorders [81].
18
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22 389 Positive and negative mood states over the past day will be measured with 12 items from the
23
24 390 circumplex model of affect [82, 83]. Momentary affect will be measured with an item for
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26
27 391 valence (“I feel unpleasant – pleasant”) and activation (“I feel aroused/activated – quiet/still”) at
28
29 392 the beginning of each diary entry. Other items cover sleep, daily activities and situations that
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31 393 may influence psychiatric symptoms, such as positive and negative events, social interactions,
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34 394 coping behaviour, physical activity and drug use.
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39 396 Follow-up measures
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41 397 Important outcomes that are linked to the above described network characteristics are
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43 398 (progression through) clinical stages, functioning and need for care. Progression through clinical
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46 399 stages will be assessed with the PQ-16, the CAPE and the CAARMS, the Symptom Check List
47
48 400 (SCL-90) [84] and the Schedules for Clinical Assessment in Neuropsychiatry, short version
49
50 401 (mini-SCAN) [85]. Social functioning will be assessed using the Groningse Vragenlijst voor
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52 402 Sociaal Gedrag (GVSG-45) [86] and the Flourishing Scale [87]. Need for care will be assessed
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55 403 using self-reported information on care use. Additionally, need for care will be assessed by
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3 404 linking data from the psychiatric case registry to our sample when approved by the participant
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5 405 (as stated on the informed consent form). Specifically, the frequency and type of care use
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8 406 throughout the study period will be obtained.
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13 408 Assessments pre- and post-daily diary period(s)

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15 409 Before and after the daily diary assessments, several questionnaires will be administered to

16
17 410 assess symptomatology, functioning and several risk and resilience factors. Psychotic symptoms

18
19 411 will be assessed with the CAPE; depression and anxiety symptoms with the Depression Anxiety

20
21 412 and Stress Scale (DASS) [88]; mania symptoms with the Altman Self-Rating Mania Scale

22
23 413 (ASRM-NL) [89], social support with the Social Support List (SLL) [90]; resilience with the

24
25 414 Brief Resilience Scale (BRS) [91] and coping style with the Utrechtse Coping Lijst (UCL) [92].

26
27 415 Furthermore, physical activity levels will be tracked with an accelerometer, the ActiCal®

28
29 416 (Respironics, Bend, OR, USA), during the first two weeks of the second diary period. Output of

30
31 417 this instrument will be presented as Energy Expenditure and Metabolic Equivalent of Task. The

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33 418 physical activity measurements are added to serve as a pilot study, and are not obligatory.
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41 420 At baseline, sleep habits will be assessed with the Munich Chronotype Questionnaire (MCTQ)

42
43 421 [93] to optimize the diary assessment process. Also, potential confounders such as smoking,

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45 422 alcohol/drug consumption, socio-economic status, Body Mass Index will be registered by means

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47 423 of a general health questionnaire. In addition, stressful life events will be assessed, using the list

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49 424 of threatening experiences [94]. Finally, pertaining to subgroup 4 only, social cognition will be

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51 425 assessed using the Faux Pas Task [95] and bonding with parents will be assessed with the
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3 426 Inventory of Parent and Peer Attachment (IPPA) [96, 97]. These factors may be of importance in
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6 427 determining a transition from an UHR status to psychosis.
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13 430 *Data analysis plan*

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15 431 To map individual symptom networks of day-to-day symptom levels, multivariate time-series

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17 432 analysis will be employed on each individual's time series data. Specifically, vector

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19
20 433 autoregression (VAR) models will be applied [98]. These models are particularly suited for

21
22 434 investigating the temporal dynamics between two or more variables. The resulting associations

23
24 435 between symptoms will subsequently be presented as networks, and network parameters will be

25
26 436 estimated. These include (but are not limited to) the strength and directionality of symptom

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28
29 437 connections (see Figure 1) and centrality indices (information about the position of a symptom in

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31 438 the network). Next, symptom networks will be compared (i) across different subgroups of

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34 439 severity and (ii) when the second diary period is completed, within each individual.
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39 441 In addition, a data-driven approach will be used to identify individuals with similar symptom

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41 442 network characteristics by (1) qualitative network comparison, (2) quantitative comparison of

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43 443 centrality indices [99, 100], and (3) longitudinal mixture models [101]. These subgroups will

44
45 444 then be compared on their levels of symptomatology and functioning and on course of

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47 445 symptomatology over time. Furthermore, the predictive value of the network parameters will be

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49 446 compared to the predictive value of usual predictors of illness course, namely cross-sectionally

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51 447 assessed level of (subclinical) psychotic pathology. Specifically, sensitivity and specificity of

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53 448 these network characteristics can be compared to sensitivity and specificity of baseline
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3 449 subclinical levels of psychotic symptoms (CAPE) and general psychopathology (SCL-90).
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6 450 Finally, risk and resilience factors, such as stressful events, social interactions, physical activity,
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8 451 coping and resilience, may also influence symptoms and, importantly, their dynamics in the
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10 452 network, but may do so differently in individuals with good or poor clinical and functional
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12 453 outcome. The role of these factors will be addressed by including them in individual network
13
14 454 analyses to examine their direct and indirect impact on symptomatology and each other.
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17 455 To control for potential confounding effects of demographic factors, such as sex, age and social
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19 456 economic status, these variables will be added as covariates to all group level analyses.
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24 458 Based on previous work [102, 103], we expect no more than 10% missing data. Missing values
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26 459 will be imputed with expectation-maximization imputation, following special recommendations
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28 460 for time-series datasets [104]. A (two-sided) p-value of 0.05 is applied for statistical testing.
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33 34 462 *Sample size and power*

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36 463 Within-person analyses: constructing individual symptom networks

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38 464 Exact sample size calculations are not possible in studies using VAR, as it is typically unclear in
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40 465 such studies what effect size can be expected. This is because the direction of causality and the
41
42 466 number of lagged influences in the system under investigation are usually unknown and
43
44 467 bidirectional and feedback effects can be present as well [98]. However, as previous work from
45
46 468 our group [102, 105, 106] and work of others [107] suggests, 60-90 measurements suffice to
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48 469 reliably identify reciprocal associations between multiple variables.
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55 471 Between-person analyses: associating symptom networks to clinical stage
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3 472 In the between-person analyses, the data have a multilevel structure. Therefore, the unilevel
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5 473 equivalent of the multilevel sample size [108] was taken to calculate the power, assuming a
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8 474 conservative intraclass-correlation of 0.8. Assuming differences of 0.05 in mean coefficients (s.d.
9
10 475 = 0.07) between the different groups [109], the proposed study has a power of 0.8 (to detect
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12 476 significant differences at $p < 0.05$). Subgroups of $N = 25$ are large enough to take into account
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14 477 effects of several covariates [110].
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19 20 479 **Ethics and dissemination**

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22 480 This study has been approved by the medical ethical committee of the University Medical Centre
23
24 481 Groningen (UMCG), Groningen, The Netherlands (registration number MEC no. 2015/159,
25
26 482 ABR no. NL52974.042.15). The study will be conducted in accordance with the Helsinki
27
28 483 Declaration, meaning that participation is voluntary and written informed consent will be
29
30 484 obtained. Several protocols have been developed for situations where clinical care may be
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32 485 warranted, e.g. in case of disclosure of suicidal thoughts, or in case of UHR status in one of the
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34 486 lower risk groups.
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41 488 An online outcome monitoring system, called RoQua (www.roqua.nl) is used for data collection
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43 489 and data storage, to which only designated researchers have access via the use of passwords
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45 490 combined with google authentication. Participants have access to the questionnaires via a link in
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47 491 their e-mail inbox. The safety of this system is guaranteed by the UMCG (an ‘In Control
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49 492 Statement’ is available on request). Data management is also organized according to UMCG
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51 493 standards, including a strict separation of identifying patient data (name, date of birth etc.) and
52
53 494 the anonymous datasets available for the researchers.
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6 496 Data gathering was not completed when this manuscript was submitted. After the study has
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8 497 ended and the study's main results have been published, the data obtained by this study will
9
10 498 become available on reasonable request. Requests should be sent to j.t.w.wigman@umcg.nl with
11
12 499 the topic name MIRORR data. The results of the study will be published in (inter)national peer-
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14
15 500 reviewed journals, presented at research, clinical and general public conferences.
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20 502 **Discussion**

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22 503 Current diagnostic systems are increasingly criticized by mental health professionals, researchers
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24 504 and users of mental health care [9, 12, 26, 111]. Conceptualization of psychopathology in terms
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27 505 of (i) clinical staging (at macro level) and (ii) dynamic, individual symptom networks (at a more
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29 506 micro level), which is the purpose of this study, represents a promising avenue to tackle both
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31 507 scientific and clinical problems. From a scientific perspective, improving our understanding of
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33
34 508 the factors driving the development of psychopathology by investigating how symptoms
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36 509 influence each other will enhance our ability to identify valid phenotypes to predict onset of
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39 510 (psychotic) mental disorders and to link with other relevant information (e.g., genetic or
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41 511 endophenotypic variation). From a clinical perspective, a better understanding of why psychotic
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43 512 symptoms can lead to a need for care in some, but resolve spontaneously in others, will help
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45
46 513 mental health professionals to adequately recognize the early needs of individuals who are likely
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48 514 to develop mental illness or functional impairments. This is important because interventions are
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50 515 both more effective and less invasive when applied early in the course of illness [112]. In more
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53 516 progressive clinical stages, deeper knowledge of the dynamic ways symptoms impact on each
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55 517 other will help to differentiate between those likely to recover or to deteriorate and between
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3 518 those likely to be responsive or resistant to treatment. Using symptom networks will improve the
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6 519 application of individually tailored, person-based interventions, adapted to one's current clinical
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8 520 stage and symptomatology, as different stages require different types of intervention. Since
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10 521 personalised interventions better fit individual needs, they will result in enhanced treatment
11
12 522 response [113], reducing the costs of mental disorders at both personal and societal level. Thus,
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14 523 the use of symptom networks will assist in improving and fine-tuning dynamic models of
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16 524 psychopathology, which will stimulate both clinical (in terms of both diagnostics and
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18 525 intervention) and scientific progress.
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49 537 **References**

- 50
51
52 538 1 van Os J, Kapur S. Schizophrenia, *The Lancet* 2009;374:635-45.
53
54 539 2 Eaton WW, Martins SS, Nestadt G, et al. The burden of mental disorders, *Epidemiol Rev*
55 540 2008;30:1-14.
56
57
58
59
60

- 1
2
3 541 3 McCrone PR, Dhanasiri S, Patel A, et al. Paying the price: the cost of mental health care in
4 542 England to 2026: King's Fund 2008.
- 5
6
7 543 4 Nationaal Kompas Volksgezondheid. Psychisch functioneren: Zijn er verschillen tussen
8 544 Nederland en andere landen? Preventie gericht op psychisch functioneren van jeugd.
- 9
10
11 545 5 Van Os J, Linscott RJ, Myin-Germeys I, et al. A systematic review and meta-analysis of the
12 546 psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of
13 547 psychotic disorder, *Psychol Med* 2009;39:179-95.
- 14
15 548 6 Wigman J, van Nierop M, Vollebergh WA, et al. Evidence that psychotic symptoms are
16 549 prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity--
17 550 implications for diagnosis and ultra-high risk research, *Schizophr Bull* 2012;38:247-57.
- 18
19
20 551 7 Wigman J, van Os J, Abidi L, et al. Subclinical psychotic experiences and bipolar spectrum
21 552 features in depression: association with outcome of psychotherapy, *Psychol Med* 2014;44:325-
22 553 36.
- 23
24
25 554 8 Kendell R, Jablensky A. Distinguishing between the validity and utility of psychiatric
26 555 diagnoses, *Am J Psychiatry* 2003.
- 27
28 556 9 Widiger TA. A dimensional model of psychopathology, *Psychopathology* 2005;38:211-4.
- 29
30
31 557 10 Widiger TA, Samuel DB. Diagnostic categories or dimensions? A question for the Diagnostic
32 558 and statistical manual of mental disorders--, *J Abnorm Psychol* 2005;114:494.
- 33
34 559 11 Kendler KS, Zachar P, Craver C. What kinds of things are psychiatric disorders? *Psychol Med*
35 560 2011;41:1143-50.
- 36
37
38 561 12 Kupfer DJ, First MB, Regier DA. A research agenda for DSM V: American Psychiatric Pub
39 562 2008.
- 40
41 563 13 Hickie IB, Scott J, McGorry PD. Clinical staging for mental disorders: a new development in
42 564 diagnostic practice in mental health, *Med J Aust* 2013;198:461-2.
- 43
44
45 565 14 Strauss JS. Hallucinations and delusions as points on continua function: Rating scale
46 566 evidence, *Arch Gen Psychiatry* 1969;21:581-6.
- 47
48
49 567 15 Haslam N, Holland E, Kuppens P. Categories versus dimensions in personality and
50 568 psychopathology: a quantitative review of taxometric research, *Psychol Med* 2012;42:903-20.
- 51
52 569 16 Kendler KS, Gardner Jr CO. Boundaries of major depression: an evaluation of DSM-IV
53 570 criteria, *Am J Psychiatry* 1998.
- 54
55
56
57
58
59
60

- 1
2
3 571 17 Angst J, Gamma A, Benazzi F, et al. Toward a re-definition of subthreshold bipolarity:
4 572 epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania, *J*
5 573 *Affect Disord* 2003;73:133-46.
6
7
8 574 18 Carter RM, Wittchen H, Pfister H, et al. One-year prevalence of subthreshold and threshold
9 575 DSM-IV generalized anxiety disorder in a nationally representative sample, *Depress Anxiety*
10 576 2001;13:78-88.
11
12
13 577 19 Krueger RF, Piasecki TM. Toward a dimensional and psychometrically-informed approach to
14 578 conceptualizing psychopathology, *Behav Res Ther* 2002;40:485-99.
15
16
17 579 20 Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during
18 580 adolescence? *Nature Reviews Neuroscience* 2008;9:947-57.
19
20 581 21 Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions
21 582 of DSM-IV disorders in the National Comorbidity Survey Replication, *Arch Gen Psychiatry*
22 583 2005;62:593-602.
23
24
25 584 22 McGorry PD, Hickie IB, Yung AR, et al. Clinical staging of psychiatric disorders: a heuristic
26 585 framework for choosing earlier, safer and more effective interventions, *Aust N Z J Psychiatry*
27 586 2006;40:616-22.
28
29
30 587 23 McGorry PD. Issues for DSM-V: clinical staging: a heuristic pathway to valid nosology and
31 588 safer, more effective treatment in psychiatry, *Am J Psychiatry* 2007.
32
33
34 589 24 Wigman JT, van Os J, Thiery E, et al. Psychiatric diagnosis revisited: towards a system of
35 590 staging and profiling combining nomothetic and idiographic parameters of momentary mental
36 591 states, *PLoS One* 2013;8:e59559.
37
38 592 25 McGorry P, van Os J. Redeeming diagnosis in psychiatry: timing versus specificity, *Lancet*
39 593 2013;381:343-5.
40
41
42 594 26 Hyman SE. The diagnosis of mental disorders: the problem of reification, *Annual review of*
43 595 *clinical psychology* 2010;6:155-79.
44
45 596 27 McGorry PD, Killackey E, Yung AR. Early intervention in psychotic disorders: detection and
46 597 treatment of the first episode and the critical early stages, *Med J Aust* 2007;187:S8-10.
47
48
49 598 28 Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition
50 599 outcomes in individuals at high clinical risk, *Arch Gen Psychiatry* 2012;69:220-9.
51
52
53 600 29 McGorry P, Keshavan M, Goldstone S, et al. Biomarkers and clinical staging in psychiatry,
54 601 *World Psychiatry* 2014;13:211-23.
55
56
57
58
59
60

- 1
2
3 602 30 Wood SJ, Yung AR, McGorry PD, et al. Neuroimaging and treatment evidence for clinical
4 603 staging in psychotic disorders: from the at-risk mental state to chronic schizophrenia, *Biol*
5 604 *Psychiatry* 2011;70:619-25.
- 6
7
8 605 31 Scott J, Leboyer M, Hickie I, et al. Clinical staging in psychiatry: a cross-cutting model of
9 606 diagnosis with heuristic and practical value, *Br J Psychiatry* 2013;202:243-5.
- 10
11
12 607 32 Keshavan MS, DeLisi LE, Seidman LJ. Early and broadly defined psychosis risk mental
13 608 states, *Schizophr Res* 2011;126:1-10.
- 14
15
16 609 33 Fusar-Poli P, Yung A, McGorry P, et al. Lessons learned from the psychosis high-risk state:
17 610 towards a general staging model of prodromal intervention, *Psychol Med* 2014;44:17-24.
- 18
19 611 34 Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, “just the facts” 4. Clinical features
20 612 and conceptualization, *Schizophr Res* 2009;110:1-23.
- 21
22
23 613 35 Lin A, Nelson B, Yung A. ‘At-risk’ for psychosis research: where are we heading?
24 614 *Epidemiology and psychiatric sciences* 2012;21:329-34.
- 25
26 615 36 van Os J. The dynamics of subthreshold psychopathology: implications for diagnosis and
27 616 treatment, *Am J Psychiatry* 2013.
- 28
29
30 617 37 Kaymaz N, Drukker M, Lieb R, et al. Do subthreshold psychotic experiences predict clinical
31 618 outcomes in unselected non-help-seeking population-based samples? A systematic review and
32 619 meta-analysis, enriched with new results, *Psychol Med* 2012;42:2239-53.
- 33
34
35 620 38 Velthorst E, Nieman D, Klaassen R, et al. Three-year course of clinical symptomatology in
36 621 young people at ultra high risk for transition to psychosis, *Acta Psychiatr Scand* 2011;123:36-42.
- 37
38
39 622 39 Zammit S, Kounali D, Cannon M, et al. Psychotic experiences and psychotic disorders at age
40 623 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study,
41 624 *Am J Psychiatry* 2013.
- 42
43
44 625 40 Kelleher I, Keeley H, Corcoran P, et al. Clinicopathological significance of psychotic
45 626 experiences in non-psychotic young people: evidence from four population-based studies, *Br J*
46 627 *Psychiatry* 2012;201:26-32.
- 47
48
49 628 41 van Rossum I, Dominguez MD, Lieb R, et al. Affective dysregulation and reality distortion: a
50 629 10-year prospective study of their association and clinical relevance, *Schizophr Bull*
51 630 2011;37:561-71.
- 52
53
54 631 42 Wigman J, Lin A, Vollebergh W, et al. Subclinical psychosis and depression: co-occurring
55 632 phenomena that do not predict each other over time, *Schizophr Res* 2011;130:277-81.
- 56
57
58
59
60

- 1
2
3 633 43 Werbeloff N, Drukker M, Dohrenwend BP, et al. Self-reported attenuated psychotic
4 634 symptoms as forerunners of severe mental disorders later in life, *Arch Gen Psychiatry*
5 635 2012;69:467-75.
- 6
7
8 636 44 Addington J, Cornblatt BA, Cadenhead KS, et al. At clinical high risk for psychosis: outcome
9 637 for nonconverters, *Am J Psychiatry* 2011;168:800-5.
- 10
11 638 45 Yung AR, Phillips LJ, Yuen HP, et al. Psychosis prediction: 12-month follow up of a high-
12 639 risk ("prodromal") group, *Schizophr Res* 2003;60:21-32.
- 13
14
15 640 46 Yung AR, Phillips LJ, Yuen HP, et al. Risk factors for psychosis in an ultra high-risk group:
16 641 psychopathology and clinical features, *Schizophr Res* 2004;67:131-42.
- 17
18
19 642 47 Demjaha A, Valmaggia L, Stahl D, et al. Disorganization/cognitive and negative symptom
20 643 dimensions in the at-risk mental state predict subsequent transition to psychosis, *Schizophr Bull*
21 644 2012;38:351-9.
- 22
23
24 645 48 Kessler RC, Birnbaum H, Demler O, et al. The prevalence and correlates of nonaffective
25 646 psychosis in the National Comorbidity Survey Replication (NCS-R), *Biol Psychiatry*
26 647 2005;58:668-76.
- 27
28
29 648 49 Breetvelt EJ, Boks MP, Numans ME, et al. Schizophrenia risk factors constitute general risk
30 649 factors for psychiatric symptoms in the population, *Schizophr Res* 2010;120:184-90.
- 31
32 650 50 Weiser M, van Os J, Davidson M. Time for a shift in focus in schizophrenia: from narrow
33 651 phenotypes to broad endophenotypes, *Br J Psychiatry* 2005;187:203-5.
- 34
35
36 652 51 Craddock N, O'Donovan MC, Owen MJ. Psychosis genetics: modeling the relationship
37 653 between schizophrenia, bipolar disorder, and mixed (or "schizoaffective") psychoses, *Schizophr*
38 654 *Bull* 2009;35:482-90.
- 39
40 655 52 Hill SK, Reilly JL, Harris MS, et al. A comparison of neuropsychological dysfunction in first-
41 656 episode psychosis patients with unipolar depression, bipolar disorder, and schizophrenia,
42 657 *Schizophr Res* 2009;113:167-75.
- 43
44
45 658 53 Bystritsky A, Nierenberg A, Feusner J, et al. Computational non-linear dynamical psychiatry:
46 659 a new methodological paradigm for diagnosis and course of illness, *J Psychiatr Res*
47 660 2012;46:428-35.
- 48
49
50 661 54 Strobl EV, Eack SM, Swaminathan V, et al. Predicting the risk of psychosis onset: advances
51 662 and prospects, *Early intervention in psychiatry* 2012;6:368-79.
- 52
53 663 55 Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive
54 664 state-of-the-art review, *JAMA psychiatry* 2013;70:107-20.
- 55
56
57
58
59
60

- 1
2
3 665 56 Barnaby N, McGorry PD, Wichers M, et al. Moving from static to dynamic models of the
4 666 onset of mental disorder, In press.
- 5
6
7 667 57 Nelson B, McGorry PD, Wichers M, et al. Moving From Static to Dynamic Models of the
8 668 Onset of Mental Disorder: A Review, *Jama psychiatry* 2017;74:528-34.
- 9
10
11 669 58 Guloksuz S, Pries L, van Os J. Application of network methods for understanding mental
12 670 disorders: pitfalls and promise, *Psychol Med* 2017:1-10.
- 13
14 671 59 Borsboom D, Cramer AO. Network analysis: an integrative approach to the structure of
15 672 psychopathology, *Annual review of clinical psychology* 2013;9:91-121.
- 16
17
18 673 60 Borsboom D, Cramer AO, Schmittmann VD, et al. The small world of psychopathology, *PloS*
19 674 *one* 2011;6:e27407.
- 20
21 675 61 van Os J, Kenis G, Rutten BP. The environment and schizophrenia, *Nature* 2010;468:203-12.
- 22
23
24 676 62 Wigman J, Kelleher I, Devlin N, et al. Coping as a moderating factor between psychotic
25 677 symptoms and functioning in adolescents with mental illness. 2013;22:S108-9.
- 26
27 678 63 Roe D, Yanos PT, Lysaker PH. Coping with psychosis: an integrative developmental
28 679 framework, *J Nerv Ment Dis* 2006;194:917-24.
- 29
30
31 680 64 Yanos P, Moos R. Determinants of functioning and well-being among individuals with
32 681 schizophrenia: an integrated model, *Clin Psychol Rev* 2007;27:58-77.
- 33
34 682 65 Barabási A, Frangos J. Linked: the new science of networks science of networks: Basic
35 683 Books 2014.
- 36
37
38 684 66 Barabási A. Bursts: the hidden patterns behind everything we do, from your e-mail to bloody
39 685 crusades: Penguin 2010.
- 40
41 686 67 Schmittmann VD, Cramer AO, Waldorp LJ, et al. Deconstructing the construct: A network
42 687 perspective on psychological phenomena, *New Ideas Psychol* 2013;31:43-53.
- 43
44
45 688 68 Yung AR, Nelson B, Thompson A, et al. The psychosis threshold in Ultra High Risk
46 689 (prodromal) research: is it valid? *Schizophr Res* 2010;120:1-6.
- 47
48
49 690 69 Oorschot M, Lataster T, Thewissen V, et al. Symptomatic remission in psychosis and real-life
50 691 functioning, *Br J Psychiatry* 2012;201:215-20.
- 51
52
53 692 70 Verma S, Subramaniam M, Abidin E, et al. Symptomatic and functional remission in patients
54 693 with first-episode psychosis, *Acta Psychiatr Scand* 2012;126:282-9.
- 55
56 694 71 Wunderink L, Nieboer RM, Wiersma D, et al. Recovery in remitted first-episode psychosis at
57 695 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment

- 1
2
3 696 strategy: long-term follow-up of a 2-year randomized clinical trial, *JAMA psychiatry*
4 697 2013;70:913-20.
5
6
7 698 72 Konings M, Bak M, Hanssen M, et al. Validity and reliability of the CAPE: a self-report
8 699 instrument for the measurement of psychotic experiences in the general population, *Acta*
9 700 *Psychiatr Scand* 2006;114:55-61.
10
11
12 701 73 Ising HK, Veling W, Loewy RL, et al. The validity of the 16-item version of the Prodromal
13 702 Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-
14 703 seeking population, *Schizophr Bull* 2012;38:1288-96.
15
16
17 704 74 Yung AR, Yung AR, Pan Yuen H, et al. Mapping the onset of psychosis: the comprehensive
18 705 assessment of at-risk mental states, *Aust N Z J Psychiatry* 2005;39:964-71.
19
20
21 706 75 Wigman JT, Vollebergh WA, Raaijmakers QA, et al. The structure of the extended psychosis
22 707 phenotype in early adolescence--a cross-sample replication, *Schizophr Bull* 2011;37:850-60.
23
24
25 708 76 Oorschot M, Kwapil T, Delespaul P, et al. Momentary assessment research in psychosis.
26 709 *Psychol Assess* 2009;21:498.
27
28
29 710 77 Myin-Germeys I, Marcelis M, Krabbendam L, et al. Subtle fluctuations in psychotic
30 711 phenomena as functional states of abnormal dopamine reactivity in individuals at risk, *Biol*
31 712 *Psychiatry* 2005;58:105-10.
32
33
34 713 78 Wigman JT, Collip D, Wichers M, et al. Altered transfer of momentary mental states
35 714 (ATOMS) as the basic unit of psychosis liability in interaction with environment and emotions,
36 715 *PLoS One* 2013;8:e54653.
37
38
39 716 79 Kroenke K, Spitzer RL, Williams JB. The Phq-9, *Journal of general internal medicine*
40 717 2001;16:606-13.
41
42
43 718 80 Zigmond AS, Snaith RP. The hospital anxiety and depression scale, *Acta Psychiatr Scand*
44 719 1983;67:361-70.
45
46
47 720 81 American Psychiatric Association. Diagnostic and statistical manual of mental disorders
48 721 (DSM-5®): American Psychiatric Pub 2013.
49
50
51 722 82 Yik M, Russell JA, Steiger JH. A 12-point circumplex structure of core affect. *Emotion*
52 723 2011;11:705.
53
54
55 724 83 Feldman Barrett L, Russell JA. Independence and bipolarity in the structure of current affect.
56 725 *J Pers Soc Psychol* 1998;74:967.
57
58
59 726 84 Derogatis LR, Unger R. Symptom checklist-90-revised, *Corsini encyclopedia of psychology*
60 727 2010.

- 1
2
3 728 85 Nienhuis FJ, van de Willige G, Rijnders CA, et al. Validity of a short clinical interview for
4 729 psychiatric diagnosis: the mini-SCAN, *Br J Psychiatry* 2010;196:64-8.
- 6
7 730 86 De Jong A, Lubbe PM. Groningse vragenlijst over sociaal gedrag:
8 731 zelfbeoordelingsvragenlijsten voor het vaststellen van problemen in het interpersoonlijke
9 732 functioneren: handleiding: Rob Giel Onderzoekcentrum 2001.
- 11
12 733 87 Diener E, Wirtz D, Tov W, et al. New well-being measures: Short scales to assess flourishing
13 734 and positive and negative feelings, *Soc Indicators Res* 2010;97:143-56.
- 15
16 735 88 Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the
17 736 Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories,
18 737 *Behav Res Ther* 1995;33:335-43.
- 20
21 738 89 Altman EG, Hedeker D, Peterson JL, et al. The Altman self-rating mania scale, *Biol*
22 739 *Psychiatry* 1997;42:948-55.
- 24
25 740 90 van Sonderen E. Sociale Steun Lijst-Interacties (SSL-I) en Sociale Steun Lijst-Discrepanties
26 741 (SSL-D): Noorderlijk Centrum voor Gezondheidsvraagstukken, Groningen 1993.
- 28
29 742 91 Smith BW, Dalen J, Wiggins K, et al. The brief resilience scale: assessing the ability to
30 743 bounce back, *Int J Behav Med* 2008;15:194-200.
- 32
33 744 92 Schreurs P, Van de Willige G. Omgaan met problemen en gebeurtenissen. De Utrechtse
34 745 Coping Lijst (UCL)(Coping with problems and events. The Utrecht Coping List (UCL)), 1998.
- 36
37 746 93 Roenneberg T, Kuehnle T, Juda M, et al. Epidemiology of the human circadian clock, *Sleep*
38 747 *Medicine Reviews* 2007;11:429-38.
- 40
41 748 94 Rosmalen J, Bos E, De Jonge P. Validation of the Long-term Difficulties Inventory (LDI) and
42 749 the List of Threatening Experiences (LTE) as measures of stress in epidemiological population-
43 750 based cohort studies, *Psychol Med* 2012;42:2599-608.
- 45
46 751 95 Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind, *J Cogn*
47 752 *Neurosci* 1998;10:640-56.
- 49
50 753 96 Armsden GC, Greenberg MT. The inventory of parent and peer attachment: Individual
51 754 differences and their relationship to psychological well-being in adolescence, *Journal of youth*
52 755 *and adolescence* 1987;16:427-54.
- 54
55 756 97 Deković M, Noom MJ, Meeus W. Expectations regarding development during adolescence:
56 757 Parental and adolescent perceptions, *Journal of youth and adolescence* 1997;26:253-72.
- 58
59 758 98 Brandt PT. Multiple time series models: Sage 2007.
- 60

- 1
2
3 759 99 Opsahl T, Agneessens F, Skvoretz J. Node centrality in weighted networks: Generalizing
4 760 degree and shortest paths, *Social networks* 2010;32:245-51.
- 6
7 761 100 Epskamp S, Cramer A, Waldorp L, et al. Qgraph: network representations of relationships in
8 762 data, *R package version 0.4* 2011;10.
- 10
11 763 101 Wit E, Abbruzzo A. Factorial graphical lasso for dynamic networks, *arXiv preprint*
12 764 *arXiv:1205.2911* 2012.
- 14
15 765 102 van Gils A, Burton C, Bos EH, et al. Individual variation in temporal relationships between
16 766 stress and functional somatic symptoms, *J Psychosom Res* 2014;77:34-9.
- 18
19 767 103 Bouwmans ME, Bos EH, Booij SH, et al. Intra-and inter-individual variability of
20 768 longitudinal daytime melatonin secretion patterns in depressed and non-depressed individuals,
21 769 *Chronobiol Int* 2015;32:441-6.
- 23
24 770 104 Honaker J, King G, Blackwell M. Amelia II: A program for missing data, *Journal of*
25 771 *statistical software* 2011;45:Retrieved from <http://www.jstatsoft.org/v45/i07>.
- 27
28 772 105 Rosmalen JG, Wenting AM, Roest AM, et al. Revealing causal heterogeneity using time
29 773 series analysis of ambulatory assessments: application to the association between depression and
30 774 physical activity after myocardial infarction, *Psychosom Med* 2012;74:377-86.
- 32
33 775 106 Bos EH, Hoenders R, de Jonge P. Wind direction and mental health: a time-series analysis
34 776 of weather influences in a patient with anxiety disorder, *BMJ Case Rep*
35 777 2012;2012:10.1136/bcr.2012-006300.
- 37
38 778 107 Lütkepohl H. New introduction to multiple time series analysis, 2005.
- 40
41 779 108 Snijders TB, Bosker R. R.(1999). Multilevel analysis: An introduction to basic and advanced
42 780 multilevel modeling.
- 44
45 781 109 Wigman JT, van Os J, Thiery E, et al. Psychiatric diagnosis revisited: towards a system of
46 782 staging and profiling combining nomothetic and idiographic parameters of momentary mental
47 783 states, *PLoS One* 2013;8:e59559.
- 49
50 784 110 Hsu LM. Random sampling, randomization, and equivalence of contrasted groups in
51 785 psychotherapy outcome research. *J Consult Clin Psychol* 1989;57:131.
- 53
54 786 111 Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new
55 787 classification framework for research on mental disorders, *Am J Psychiatry* 2010;167:748-51.
- 57
58 788 112 McGorry PD, Hickie IB, Yung AR, et al. Clinical staging of psychiatric disorders: a
59 789 heuristic framework for choosing earlier, safer and more effective interventions, *Aust N Z J*
60 790 *Psychiatry* 2006;40:616-22.

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3 791 113 Boertien D. Herstel en empowerment (Recovery and empowerment). In: Veling W, Van der
4 792 Wal M, Jansen S, et al., eds. Handboek Vroege Psychose (Manual for early psychosis) 2013.

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11 795 **Authors' contributions**

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13 796 JTWW conceived the study. JTWW and SHB designed and are executing the study and drafted
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15 797 the first versions of the manuscript. LW, PdJ, JvO, MCW helped conceptualize the study and
16
17 798 provided general advice and input, SS contributed to the study design, specifically to the data
18
19 799 gathering and data management part. All authors critically reviewed the manuscript, and
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21 800 collaborated in the discussion of the intellectual content of the manuscript. All authors read and
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23 801 approved the final manuscript.
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46 810 **Competing interests**

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48 811 The authors declare that they have no competing interests.
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814 **Tables**

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815 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	T1	T1	T1	T2	T3
							(3m)			(3m)		
<i>Demo-graphics</i>	Gen. Health	SR	Demogr, conf.	5	X				X [†]			
	Vignette	INT	History psychosis	5	X**							
<i>Psychosis</i>	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* [†]
<i>Psychopathology</i>	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		

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Table 1. Continued.

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
<i>Social functioning</i>	GVSG-45	SR	Social functioning	8		X		X			X	X
	Flourishing Sc	SR	Well-being	1		X		X			X	X
<i>Risk & resilience</i>	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***		

816 Note. SR = Self-report, INT = Interview, REG = register, SENS = sensor Sx = symptoms, demogr = demographics, conf =

817 confounders, depress = depression, T = measurement wave, m = months.

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3 818 * Only administered when PQ score is 6 or higher.
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6 819 ** Only administered when there is a history of a psychiatric disorder according to the information on the General Health
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9 820 Questionnaire
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12 821 *** Offered to participants as optional.
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15 822 † Available as ROM data for all individuals in clinical care for mental health at each measurement wave.
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18 823 ‡ Send out several weeks before the daily diary period to screen on exclusion criteria
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22 824 # Administered only to subgroup 4
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3 826 **Figure titles and legends**
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10 828 Figure 1. Parameters of a theoretical symptom network.
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13 829 Note. This figure is for illustrative purposes, and is not based on real data.
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22 832 Figure 2. Flowchart.
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26 833 Note. Light grey area within blue dashed square indicates optional measurements.
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35 836 Figure 3. Definition of subgroups.
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3 838 **Additional files**
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13 841 Title: Table S1. Diary items
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16 842 Description: Original Dutch diary items and their translation to English
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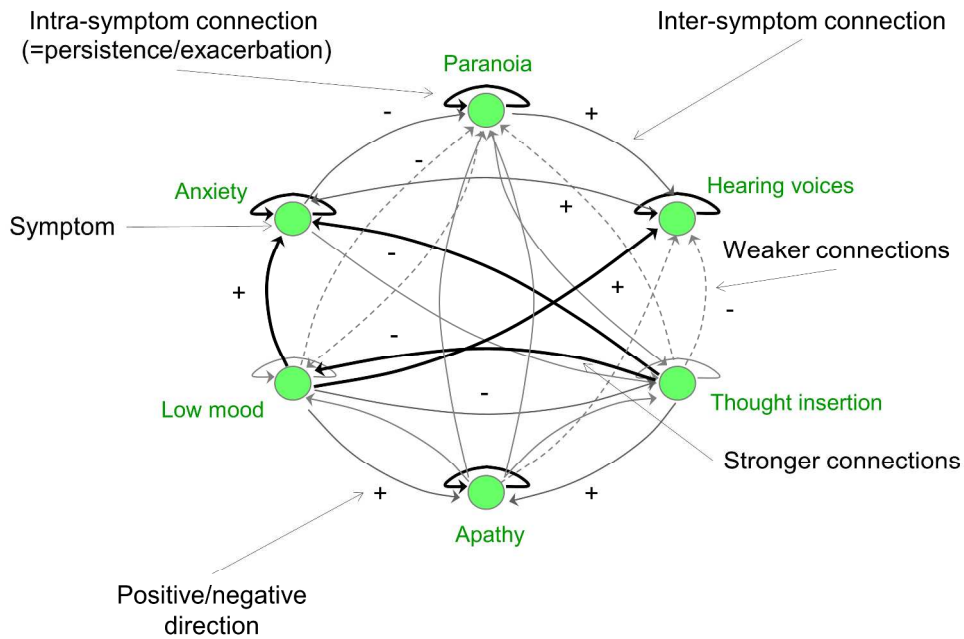


Figure 1. Parameters of a theoretical symptom network. Note. This figure is for illustrative purposes, and is not based on real data.

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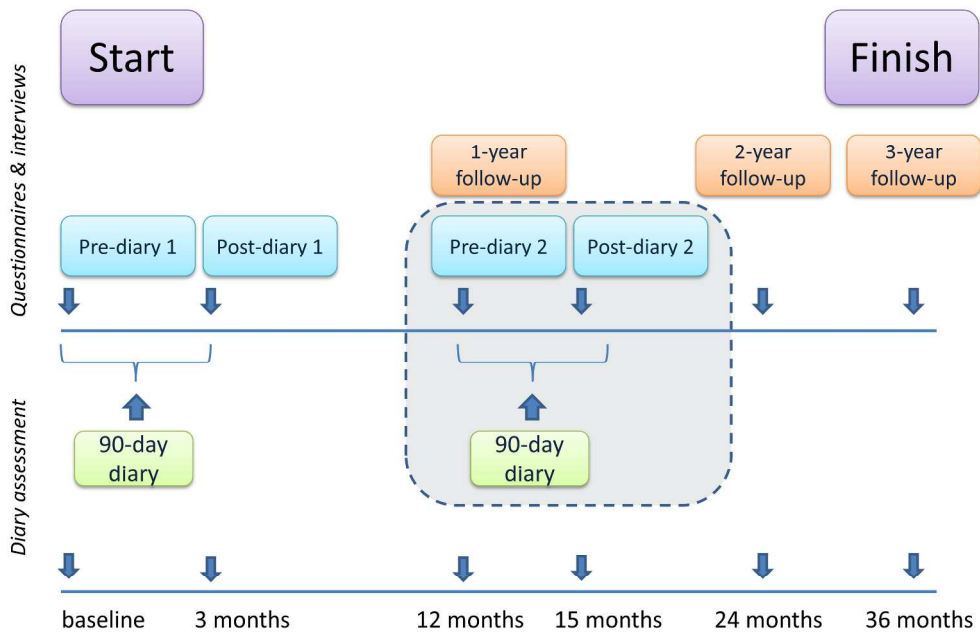


Figure 2. Flowchart. Note. Light grey area within blue dashed square indicates optional measurements.

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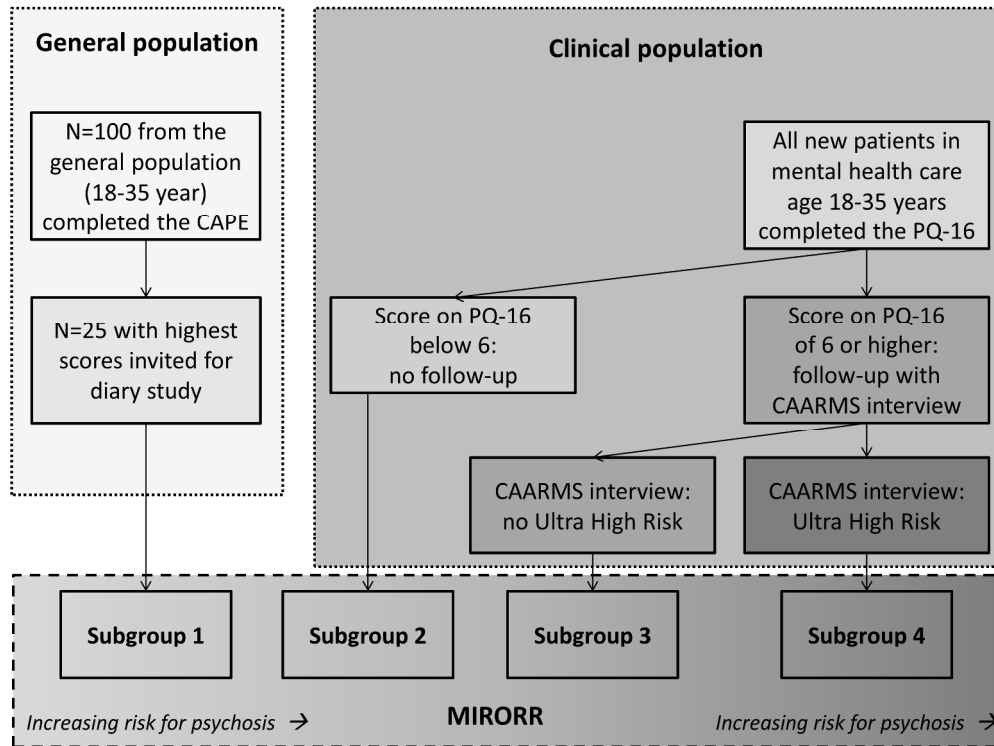


Figure 3. Definition of subgroups.

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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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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

1		geslapen?				
2						
3						
4	10	Hoeveel uur heb je	About how many	Hours, minutes	0 - 24	Sleep
5		afgelopen nacht	hours did you sleep			
6		ongeveer geslapen?	tonight?			
7						
8	11	Heb je vandaag	Did you sleep during	• No (skip to 13)	0 - 1	Sleep
9		overdag geslapen?	the day today (naps)?	• Yes		
10		(dutjes)				
11	12	Hoe lang in totaal?	How long in total did	Hours, minutes	0 - 12	Sleep
12			you sleep during the			
13			day today?			
14						
15	<i>Instruction</i>	<i>Alle items gaan</i>	<i>From now on, all</i>			
16		<i>vanaf nu over de</i>	<i>items involve the past</i>			
17		<i>afgelopen dag (denk</i>	<i>day (think about how</i>			
18		<i>aan hoe je je</i>	<i>you felt on average</i>			
19		<i>vandaag gemiddeld</i>	<i>today)</i>			
20		<i>voelde)</i>				
21						
22	13	Ik voelde me	I felt relaxed today	Not at all – Very much	0 – 100	Positive
23		vandaag ontspannen				deactivation
24	14	Ik voelde me	I felt calm today	Not at all – Very much	0 – 100	Positive
25		vandaag kalm				deactivation
26	15	Ik voelde me	I felt satisfied today	Not at all – Very much	0 – 100	Positive
27		vandaag tevreden				deactivation
28	16	Ik voelde me	I felt energetic today	Not at all – Very much	0 – 100	Positive
29		vandaag energiek				activation
30	17	Ik voelde me	I felt enthusiastic	Not at all – Very much	0 – 100	Positive
31		vandaag enthousiast	today			activation
32	18	Ik voelde me	I felt cheerful today	Not at all – Very much	0 – 100	Positive
33		vandaag opgewekt				activation
34	19	Ik voelde me	I felt apathetic today	Not at all – Very much	0 – 100	Negative
35		vandaag lusteloos				deactivation
36	20	Ik voelde me	I felt tired today	Not at all – Very much	0 – 100	Negative
37		vandaag moe				deactivation
38	21	Ik voelde me	I felt down today	Not at all – Very much	0 – 100	Negative
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	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

1						
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3	35	Ik vond mijn leven	I found my life was	Not at all – Very much	0 – 100	Worthlessness
4		vandaag de moeite	worthwhile today			
5		waard				
6						
7	36	Ik had vandaag last	I was bothered by	Not at all – Very much	0 – 100	Physical
8		van lichamelijke	physical symptoms			discomfort
9		klachten	today			
10	37	Ik had vandaag de	Today I had the	Not at all – Very much	0 – 100	Disorganized
11		neiging iets	tendency to do			thoughts
12		onbeheersts te doen	something			
13			unrestrained/wild			
14						
15	38	Mijn gedachten	My thoughts wouldn't	Not at all – Very much	0 – 100	Disorganized
16		lieten me vandaag	leave me alone today			thoughts
17		niet los				
18						
19	39	Mijn gedachten	My thoughts were	Not at all – Very much	0 – 100	Disorganized
20		waren vandaag	racing today			thoughts
21		versneld				
22						
23	40	Mijn gedachten	My thoughts were	Not at all – Very much	0 – 100	Disorganized
24		waren vandaag	difficult to express			thoughts
25		moeilijk te uiten	today			
26	41	Er is vandaag iets	Today something	Not at all – Very much	1 – 7	Strange
27		vreemds met mij of	strange happened to			impressions /
28		om mij heen	me or around me that			Delusions
29		gebeurd dat ik	was difficult for me to			
30		moeilijk kon	explain			
31		verklaren				
32						
33	42	Ik hoorde vandaag	Today I heard voices	Not at all – Very much	1 – 7	Hallucinations
34		stemmen die	that others couldn't			
35		anderen niet	hear			
36		hoorden				
37						
38	43	Ik zag vandaag	Today I saw things	Not at all – Very much	1 – 7	Hallucinations
39		dingen die anderen	that others couldn't			
40		niet zagen	see			
41	44	Ik had vandaag het	Today I had the	Not at all – Very much	0 – 100	Paranoia
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4		gevoel dat anderen	feeling that others did		
5		me niet mochten	not like me		
6	45	Ik had vandaag het	I felt that others could	Not at all – Very much	0 – 100 Delusions
7		gevoel dat anderen	read my thoughts		
8		mijn gedachten	today		
9		konden lezen			
10	46	Ik voelde me	I felt unreal today	Not at all – Very much	0 – 100 Delusions
11		vandaag			
12		onwerkelijk			
13	47	Ik had vandaag het	I felt that others could	Not at all – Very much	0 – 100 Delusions
14		gevoel dat anderen	control me today		
15		controle over me			
16		uitoefenden			
17	48	Ik kon vandaag	I could experience	Not at all – Very much	0 – 100 Flat affect
18		plezier ervaren	pleasure when nice		/anhedonia
19		wanneer er leuke	things happened today		
20		dingen gebeurden			
21	49	Er kwam vandaag	I did not get many	Not at all – Very much	0 – 100 Motivation /
22		weinig uit mijn	things done today		drive
23		handen			
24	50	Ik had vandaag zin	I felt like undertaking	Not at all – Very much	0 – 100 Motivation /
25		om dingen te	something to day		drive
26		ondernemen			
27	51	Ik deed dingen ‘op	I did things on	Not at all – Very much	0 – 100 Mindfulness
28		de automatische	automatic without		
29		piloot’, zonder mij	being conscious of		
30		erg bewust te zijn	what I was doing		
31		van wat ik aan het	today		
32		doen was			
33	52	Mijn eetlust was	My appetite today was	Smaller than normal – Larger than normal	0 – 100 Appetite
34		vandaag			
35	53	Hoe gestrest was je	How stressed were	Not at all – Very much	0 – 100 Stress
36		vandaag?	you today?		
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3	54	In welke mate zijn	To what extent did	Not at all – Very much	0 – 100 Positive events
4		er vandaag positieve	positive events happen		
5		gebeurtenissen	today?		
6		geweest?			
7					
8	<i>Instruction</i>	<i>Denk aan de</i>	<i>Think about the most</i>		
9		<i>belangrijkste</i>	<i>important positive</i>		
10		<i>positieve</i>	<i>event of today</i>		
11		<i>gebeurtenis van de</i>			
12		<i>afgelopen dag</i>			
13					
14	55	Hoe plezierig was	How pleasant was this	Neutral – Very pleasant	0 – 100 Positive events
15		deze gebeurtenis?	event?		
16	56	Hoe belangrijk was	How important was	Very unimportant – Very important	0 – 100 Positive events
17		deze gebeurtenis	this positive event to		
18		voor mij?	me?		
19					
20	57	Was deze positieve	Was this positive	• No (skip to 59)	0 - 1 Positive events
21		gebeurtenis	event planned?	• Yes	
22		gepland?			
23					
24	58	Ik keek er naar uit	I was looking forward	Not at all – Very much	0 – 100 Positive events
25			to it		
26	59	In welke mate zijn	To what extent did	Not at all – Very much	0 – 100 Negative events
27		er vandaag	negative events		
28		negatieve	happen today?		
29		gebeurtenissen			
30		geweest?			
31					
32	<i>Instruction</i>	<i>Denk aan de</i>	<i>Think about the most</i>		
33		<i>belangrijkste</i>	<i>important negative</i>		
34		<i>negatieve</i>	<i>event of today</i>		
35		<i>gebeurtenis van de</i>			
36		<i>afgelopen dag</i>			
37					
38	60	Hoe onplezierig was	How unpleasant was	Very unpleasant - Neutral	0 – 100 Negative events
39		deze gebeurtenis?	this event?		
40	61	Hoe belangrijk was	How important was	Very unimportant – Very important	0 – 100 Negative events
41		deze gebeurtenis	this negative event to		
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4	62	voor mij? Was deze negatieve gebeurtenis gepland?	me? Was this negative event planned?	<ul style="list-style-type: none"> • No (skip to 59) • Yes 	0 - 1	Negative events
5						
6						
7						
8						
9	63	Ik zag er tegen op	I dreaded it	Not at all – Very much	0 – 100	Negative events
10						
11	64	Welke gebeurtenis was het meest spannend of stressvol?	Which event was most exciting or stressful?	<ul style="list-style-type: none"> • The negative event • The positive event 	1 - 2	Event stressfulness
12						
13						
14						
15	65	Hoe stressvol of spannend was deze gebeurtenis?	How stressful or exciting was this event?	Not at all – Very much	0 – 100	Event stressfulness
16						
17						
18						
19	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	<ul style="list-style-type: none"> • 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
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35	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
36						
37						
38						
39						
40	68	Ik was liever wat meer in gezelschap	I would have preferred more company	Not at all – Very much	0 – 100	Social context
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1		geweest				
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4		Ik vond het	I found today's	Very unpleasant – Very pleasant	0 – 100	Social context
5	69	gezelschap van	company mostly			
6		vandaag				
7		overwegend				
8						
9	70	Voelde je je	Did you feel supported	Not at all – Very much	0 – 100	Social context
10		vandaag gesteund?	today?			
11	71	Ik had liever meer	I would have liked to	Not at all – Very much	0 – 100	Social context
12		steun gevoeld	feel more support			
13	72	Heb je vandaag met	Have you had a	<ul style="list-style-type: none"> • No (skip to 78) • Yes 	0 – 1	Social context
14		iemand een gesprek	conversation with			
15		gevoerd?	someone today?			
16	<i>Instruction</i>	<i>Denk aan het voor</i>	<i>Think about the most</i>			
17		<i>jou belangrijkste</i>	<i>important</i>			
18		<i>gesprek van</i>	<i>conversation of today</i>			
19		<i>vandaag (mag ook</i>				
20		<i>via telefoon of</i>				
21		<i>mobiele</i>				
22		<i>berichtenapp)</i>				
23						
24	73	Met wie was dit	With whom was this	<ul style="list-style-type: none"> • Family (except partner) <ul style="list-style-type: none"> ○ Father ○ Mother ○ Other • Partner • Friend • Other 	1 - 7	Social context
25		gesprek?	conversation?			
26						
27						
28						
29						
30						
31						
32						
33						
34						
35	74	Hoe kritisch was	How critical was this	Not at all – Very much	0 – 100	Expressed emotions
36		deze persoon naar	person towards you?			
37		jou toe?				
38	75	Hoe warm was deze	How warm was this	Not at all – Very much	0 – 100	Expressed emotions
39		persoon naar jou	person towards you?			
40		toe?				
41						
42	76	In welke mate	To what extent did this	Not at all – Very much	0 – 100	Expressed
43						
44						
45						
46						
47						
48						
49						

	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	<ul style="list-style-type: none"> • 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
<i>Instruction</i>	<i>Het volgende item gaat over morgen</i>	<i>The next item is about tomorrow</i>			
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>.