

1 **Exploring the Predictive Power of the Unspecific Risk Category**
2 **(URC) of the Basel Screening Instrument for Psychosis (BSIP)**

3 *Running title: Unspecific risk for psychosis*

4

5 David Peralta^{1,2}, Erich Studerus¹, Christina Andreou¹, Katharina Beck^{1,3}, Sarah Ittig¹, Letizia
6 Leanza^{1,3}, Laura Egloff^{1,3}, Anita Riecher-Rössler^{1*}

7

8 ¹University of Basel Psychiatric Hospital, Center for Gender Research and Early Detection, Basel,
9 Switzerland

10 ²Zamudio Psychiatric Hospital, Mental Health Network of Biscay (Osakidetza), Bilbao, Spain

11 ³University of Basel, Department of Psychology, Division of Clinical Psychology and Epidemiology

12

13

14

15 ***Corresponding Author**

16 Prof. Anita Riecher-Rössler, MD PhD
17 Head of Center for Gender Research and Early Detection
18 Psychiatric University Clinics Basel
19 Wilhelm Klein-Strasse 27
20 CH-4002 Basel
21 Tel.: +41 61 325 59 95
22 E-mail: Anita.Riecher@upkbs.ch

23

24 **Abstract**

25 **Aim:** The Ultra High Risk (UHR) criteria, consisting of Brief Limited Intermittent Psychotic
26 Symptoms (BLIPS), Attenuated Psychotic Symptoms (APS) and Genetic Risk and
27 Deterioration Syndrome (GRD) are the most widely used criteria for assessing the At-Risk
28 Mental State (ARMS) for psychosis. The Basel Screening Instrument for Psychosis (BSIP)
29 includes a further risk category, the Unspecific Risk Category (URC). However, little is known
30 about the predictive power of this risk category compared to other risk categories.

31 **Methods:** Two hundred ARMS patients were detected as part of the **FePsy** (*Früherkennung*
32 von **Ps**ychosen) study using the BSIP. Transition to psychosis was assessed in regular
33 intervals for up to 7 years.

34 **Results:** Patients meeting only the URC criterion ($n = 40$) had a significantly lower risk of
35 transition to psychosis than the UHR group (including BLIPS, APS and GRD) (HR 0.19 [0.05;
36 0.80] $p=0.024^*$). Furthermore, the URC only risk group had a lower transition risk than the
37 APS without BLIPS group ($p= 0.015$) and a trendwise lower risk than the BLIPS group
38 ($p=0.066$). However, despite the lower transition risk in the URC only group, there were still 2
39 patients (5%) in this group with a later transition to psychosis.

40 **Conclusions:** The URC includes patients who have a lower risk of transition than those
41 included by the UHR categories and thereby increases the sensitivity of the BSIP. This offers
42 the possibility of a stratified intervention, with these subjects receiving low intensity follow up
43 and treatment.

44 **KEYWORDS:** follow-up studies; prodromal symptoms; psychotic disorders; risk; sensitivity
45 and specificity

46

47 **1. INTRODUCTION**

48

49 There is increasing evidence that intervention in a potential prodromal phase of psychosis
50 can lead to improved outcomes in many domains (McGorry et al., 2009; Riecher-Rössler,
51 McGorry, & Sartorius, 2016). Several clinical instruments have been developed to capture
52 the potential prodromal phase of a psychotic disorder, leading to operationalized criteria for
53 clinical high risk (CHR) or at-risk mental states (ARMS) (Fusar-Poli, Borgwardt, Bechdolf, &
54 et al., 2013). The major approach to psychosis prediction in the last two decades was based
55 on the Ultra High Risk criteria (UHR), focusing mainly on “prepsychotic symptoms” i.e.,
56 Attenuated Psychotic Symptoms (APS), Brief Limited Intermittent Psychotic Symptoms
57 (BLIPS) and the so called “genetic risk and deterioration syndrome” (GRD); patients meeting
58 UHR criteria show transition rates of up to 36% after 3 years of initial presentation (Fusar-
59 Poli, Bonoldi, Yung, & et al., 2012). Another important line of research has been the Basic
60 Symptom (BS) approach, which focuses on subjectively perceived cognitive and sensory
61 changes that are qualitatively different from positive psychotic symptoms (Klosterkötter,
62 Hellmich, Steinmeyer, & Schultze-Lutter, 2001). These are thought to represent an earlier
63 risk stage (Schultze-Lutter, Ruhrmann, Berning, Maier, & Klosterkötter, 2010).

64 Instruments assessing psychosis risk based on UHR and BS criteria in help seeking patients
65 show excellent sensitivity but only modest specificity, with high rates of false positives
66 (Fusar-Poli et al., 2015). However, several studies have shown that this can be improved by
67 integrating further clinical, neurobiological and environmental factors into prediction models
68 (Riecher-Rössler & Studerus, 2017). For example, specific aspects of psychopathology,
69 social decline, and neurocognitive impairment have shown to be suitable candidates for
70 multidomain assessment and increase of predictive power (Cannon et al., 2016; Riecher-
71 Rössler et al., 2013; Riecher-Rössler et al., 2009).

72 The Basel Screening Instrument for Psychosis (BSIP) was developed in the late 1990's by
73 (Riecher-Rössler et al., 2008) with the aim of identifying not only patients at “Ultra High Risk”

74 (i.e., suffering from BLIPS, APS or GRD) but also patients thought to be at lower risk
75 because of having less specific prodromal symptoms and risk factors for psychosis. A
76 combination of these factors constitutes the Unspecific Risk Category (URC) of the BSIP.
77 Specifically, it consists of the nine DSM-III-R (Diagnostic and Statistical Manual of Mental
78 Disorders, 3rd edition-Revised) (American Psychiatric Association, 1987) prodromal
79 symptoms and other unspecific prodromal symptoms and risk factors found in previous
80 studies (Riecher-Rössler et al., 2008; Riecher-Rössler et al., 2006). The BSIP thus allows to
81 assess the UHR criteria following Yung et al. (1998) and in addition to that defines a low risk
82 or unspecific risk category. The instrument has been demonstrated to have a high predictive
83 validity and reliability (Riecher-Rössler et al., 2008) and ARMS patients identified by the
84 BSIP have shown transition rates that are comparable to those reported by other groups
85 (Riecher-Rössler et al., 2013; Riecher-Rössler et al., 2008). An English translation of the
86 BSIP can be found in the supplementary material.

87 The creation of the URC was based on research findings reporting that up to 73% of patients
88 later diagnosed as having schizophrenia had shown unspecific or negative symptoms before
89 manifesting overt psychotic symptoms (Häfner et al., 1998). However, many URC symptoms
90 overlap with those of other mental disorders and therefore they lack specificity. It was
91 hypothesized that a combination of these symptoms with other known risk factors (e.g.,
92 social decline, drug use, previous behavioral or psychiatric problems and/or genetic risk)
93 could indicate an increased risk of psychosis in help seeking individuals. To date, the
94 predictive accuracy of the URC and its single components remains unknown and the
95 predictive performance of DSM-III-R prodromal symptoms has only been tested
96 retrospectively in psychotic patients (Jackson, McGorry, & Dudgeon, 1995).

97 Thus, the main objective of the study was to assess the predictive value of the URC of the
98 BSIP for a later transition to psychosis as compared to the more widely established UHR
99 criteria. A second goal was to assess the predictive performance of the individual items
100 comprised in the URC. Due to the unspecific nature of the symptoms and risk factors

101 comprised in the URC, we hypothesized that patients meeting only the URC would show a
102 lower risk of transition to psychosis than patients meeting any of the UHR criteria.

103

104 **2. METHODS**

105 **2.1 Setting and recruitment**

106 Study participants were recruited between March 1, 2000 and May 31, 2017 as part of the
107 prospective “Früherkennung von Psychosen” (**FePsy**; English: early detection of psychosis)
108 study. A detailed description of the study design can be found elsewhere (Riecher-Rössler et
109 al., 2007; Riecher-Rössler et al., 2009). In brief, patients suspected to be in their early
110 (prodromal) phase of psychosis were referred to our specialized early detection clinic at the
111 University of Basel Psychiatric Hospital, Switzerland. To encourage early, low threshold
112 referrals, widespread information campaigns were performed during the study period
113 targeting both potential referring professionals and lay people. Risk check-lists for referrals
114 and self-screening instruments were developed and distributed as described in detail in
115 previous publications (Müller et al., 2010; Riecher-Rössler et al., 2013). After complete
116 description of the study to the subjects, written informed consent was obtained. The study
117 was approved by the ethics committee of North-western and Central Switzerland (EKNZ) and
118 conforms to the provisions of the declaration of Helsinki of 1975, as revised in 2008.

119 Patients were included into this study if they met ARMS criteria (see below) and did not meet
120 any of the following exclusion criteria: age below 18 years, insufficient knowledge of German,
121 IQ < 70, previous episode of schizophrenic psychosis (treated with antipsychotics for >3
122 weeks or exceeding lifetime cumulative chlorpromazine equivalent dose of 2500 mg),
123 psychosis clearly due to organic reasons or substance abuse, or psychotic symptomatology
124 within a clearly diagnosed affective psychosis or borderline personality disorder.

125

126 **2.2 Screening**

127 All patients referred to our early detection center were screened with the Basel Screening
128 Instrument for Psychosis (BSIP). A detailed description of the instrument can be found in a
129 previous publication (Riecher-Rössler et al., 2008). The English version of the BSIP is
130 available online as Supporting Information. Briefly, this instrument allows assessing pre-
131 psychotic and psychotic symptoms but also includes early prodromal symptoms as specified
132 in the DSM-III-R (American Psychiatric Association, 1987) and other unspecific potential
133 prodromal symptoms and risk factors for psychosis as reported in literature such as young
134 age, drug abuse, psychoses in family members or social decline (Riecher-Rössler et al.,
135 2008; Riecher-Rössler et al., 2006). It includes 7 domains of symptoms, signs and risk
136 factors. The BSIP has shown a good inter-rater reliability ($\kappa = 0.67$) for the assessment of the
137 main outcome category “at-risk for psychosis” and a high predictive validity (Riecher-Rössler
138 et al., 2008).

139 Inclusion as ARMS patient occurred if one of the following criteria was met: (1) Prepsychotic
140 category: APS or BLIPS according to criteria by Yung et al. (1998); (2) Genetic risk category
141 (GRC): genetic risk in combination with 2 or more other risk factors such as social decline;
142 (3) Unspecific Risk Category (URC): a certain combination of risk factors according to the
143 screening instrument. A more precise description of the risk categories is accessible in the
144 English version of the BSIP (see Supporting Information). Patients classified under
145 categories (1) and (2) are considered at “high risk” because they show more psychosis-
146 related symptoms or risk factors, whereas patients in category (3) show rather unspecific
147 symptoms and risk factors and are thus considered as having a “lower risk”.

148 Patients were classified as having an ARMS, as not having an ARMS or as having an
149 established first episode psychosis.

150

151

152 **2.3 Assessment of current psychopathology**

153 In addition to screening with the BSIP, patients were examined on other aspects of
154 psychopathology. Negative symptoms were assessed with the Scale for the Assessment of
155 Negative Symptoms (SANS) (Andreasen, 1989) and positive and disorganized symptoms
156 were examined with the Brief Psychiatric Rating Scale- Expanded version (BPRS- E)
157 (Ventura et al., 1993). BPRS subscales were calculated according to the five-factor model
158 recently proposed by Dazzi, Shafer, and Lauriola (2016).

159 **2.4 Follow up**

160 If patients fulfilled criteria for having an ARMS they were asked to take part in further multi-
161 domain assessments and in a follow-up study. Patients who agreed to participate were
162 reassessed at regular intervals for up to 7 years to examine whether transition to psychosis
163 had occurred. Transition to psychosis was assessed according to the criteria of Yung et al.
164 (1998) using the four BPRS items “suspiciousness”, “unusual thought content”,
165 “hallucinations” and “conceptual disorganization”. During the first year of the follow-up,
166 ARMS patients were assessed monthly, during the second and third years every 3 months,
167 and thereafter annually.

168 **2.5. Statistical analyses**

169 All analyses were performed using the R environment for statistical computing (R
170 Development Core Team, 2017). The predictive potential of baseline sociodemographic and
171 clinical variables, as well as of different risk groups, was investigated using survival analysis
172 methods. Survival models are more appropriate than binary outcome (i.e., transition vs. non-
173 transition) models in prospective studies with longer-term diagnostic outcomes and regular
174 follow-up assessments because they not only take transition vs. non-transition into account
175 but also the time to transition and thus have more statistical power (van der Net et al., 2008).
176 Furthermore, whereas binary outcome models must exclude patients with short follow-up
177 duration, which leads to further reduced power and potentially unrepresentative samples,

178 survival models do not suffer from this problem because they can treat patients with
179 incomplete follow-up as censored observations (i.e., patients can still provide information for
180 estimating the probability of transition up to the time they were followed up). For binary and
181 continuous independent variables, we used log-rank and cox proportional hazard models,
182 respectively.

183 Since the four risk criteria of the BSIP had large overlaps, we stratified study participants
184 hierarchically based on the fulfillment of four non-overlapping conditions: 1) BLIPS; 2) APS,
185 but not BLIPS; 3) GRD, but not APS or BLIPS; and 4) URC, but not BLIPS, APS, or GRD
186 (i.e., URC only). We then performed log-rank tests to compare the rate of transition to
187 psychosis between the URC only group and groups 1 to 3 individually and combined.

188

189 **3. RESULTS**

190 **3.1 Baseline demographic and clinical characteristics**

191 745 patients with suspected ARMS were screened of whom 310 were identified as having an
192 ARMS. Of these, 200 provided written informed consent and thus were included into this
193 study. Forty-four (22%) of these patients transitioned to psychosis within the follow-up period
194 (ARMS-T) and 156 did not (ARMS-NT). Mean follow-up time was 3.04 years (median 2.66,
195 range 0.03-7.00) for ARMS-NT patients and 1.35 years (median 0.77, range 0.01-6.51) for
196 ARMS-T patients.

197 The frequencies of different risk categories, as well as their overlap, are presented in **Figure**
198 **1.** All patients fulfilling APS or BLIPS criteria also met the URC criterion. Among those in the
199 GRD category all except two also met the URC criterion. Forty (20%) patients were only
200 included because they had a combination of unspecific risk factors, that is, because they met
201 the URC only criterion.

202 Socio-demographic and clinical characteristics at baseline of the total study sample, as well
 203 as of ARMS-T and ARMS-NT patients, are shown in **Table 1**. None of the sociodemographic
 204 variables were significantly associated with later transition to psychosis. However, higher
 205 scores at baseline in the BPRS total score, in the BPRS subscales of “positive symptoms”
 206 and “disorganization” significantly increased the risk of transition to psychosis ($p = 0.037$, $p =$
 207 0.001 and $p = 0.011$ respectively).

208 When the sample of ARMS patients was stratified hierarchically (BLIPS, APS but not BLIPS,
 209 GRD but not APS or BLIPS, URC only), risk criteria were distributed as follows: 15 (7.5%)
 210 patients met the BLIPS criterion, 128 (64%) had APS but not BLIPS, 17 (8.5%) had GRD but
 211 not APS or BLIPS, and 40 (20%) met the URC only criterion (**Table 2**).

212 **3.2 Differences in transition rates across risk categories**

213 Patients meeting the URC only criterion had a significantly lower risk of transition to
 214 psychosis than all other risk groups combined (HR 0.19 [0.05; 0.80] $p = 0.024^*$).
 215 Furthermore, the URC only risk group had a lower transition risk than the APS without BLIPS
 216 group ($p = 0.015$) and a trendwise lower risk than the BLIPS group ($p = 0.066$) (**Table 2**).

217 **Figure 2** shows the Kaplan-Meier estimates of the proportion of patients remaining non-
 218 psychotic for each of the four risk categories (stratified hierarchically).

219 **3.3 Individual items of the URC**

220 Among the individual items comprised in the URC criterion, within the total group of all
 221 patients, only the item “*ever experienced psychotic or attenuated psychotic symptoms*”
 222 showed a significant increase of risk for transition to psychosis (HR 6.70 [1.62; 27.7] $p =$
 223 0.009**). The DSM-III-R prodromal symptom “*odd beliefs*” showed a trend towards increased
 224 risk (HR 1.76 [0.96; 3.21] $p = 0.066$). None of the other items seemed to significantly
 225 increase the risk individually. However, most of the items had a greater prevalence among
 226 subjects who later transitioned to psychosis than among those who did not transition (**Table**
 227 **3**).

228 **4. DISCUSSION**

229 The present study investigated the predictive power for transition to psychosis of different
230 ARMS categories identified with the BSIP in patients followed-up for up to 7 years. Recent
231 studies have shown that the construct of ARMS is not homogeneous (Fusar-Poli et al., 2016)
232 and that clinical staging or stratification of risk may be necessary to better plan and
233 individualize treatment strategies (Cannon et al., 2016; Fusar-Poli, 2017). Accordingly, we
234 found that high risk categories yielded very heterogeneous results regarding transition to
235 psychosis. The fact that none of the patients meeting the GRD criterion (without APS or
236 BLIPS) transitioned to psychosis is in line with recent findings showing that this category
237 may not be suitable for risk prediction, at least in the short-term, and that it should be viewed
238 as a different class of risk (Fusar-Poli et al., 2016; Schultze-Lutter et al., 2015). The APS
239 category is nowadays the most frequently found in ARMS samples and the most solidly
240 supported risk category of the ARMS construct (Cornblatt & Carrion, 2016) and it is being
241 used as the main category in novel clinical staging models (Carrion, Correll, Auther, &
242 Cornblatt, 2017). In accordance with this, we found that APS was the most prevalent risk
243 group in our sample of ARMS patients and that its presence significantly increased the risk of
244 transition to psychosis.

245 The main aim of the study, however, was to assess the predictive power of the URC criterion
246 with regards to psychosis transition. We could confirm the hypothesis that this category
247 included individuals with a considerably lower risk of transition than the UHR group. This is
248 probably due to the fact that some of the symptoms and risk factors of the URC (e.g., social
249 isolation, lack of initiative, impaired role functioning, drug use) are also important features of
250 common mental disorders such as depression and anxiety (Horneland, Vaglum, & Larsen,
251 2002). Nevertheless, it is well known that the prodromal phase of psychotic disorders is
252 characterized by many of these unspecific symptoms (Häfner et al., 1998; Häfner, Riecher-
253 Rössler, Hambrecht, et al., 1992; Häfner, Riecher-Rössler, Maurer, Fätkenheuer, & Löffler,
254 1992; Riecher-Rössler et al., 2006). Therefore, attributing these manifestations of

255 psychopathology to a possibly emerging psychotic illness can be a challenging task (Aston et
256 al., 2012). The high rates of comorbidity in ARMS patients, especially with depressive
257 disorders (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014), create a picture of mixed
258 early subthreshold symptoms (some with psychotic expression), with some authors
259 proposing a transdiagnostic model for the early assessment (Cuesta & Peralta, 2008;
260 McGorry & Nelson, 2016; Riecher-Rössler & Studerus, 2017; van Os & Guloksuz, 2017).
261 Additionally, in our sample, we could not demonstrate that any individual item comprising the
262 URC was significantly associated with later transition to psychosis, except for the item “ever
263 experienced psychotic or attenuated psychotic symptoms”. This may reflect the fact that this
264 item is largely overlapping with APS or BLIPS risk criteria (i.e., patients meeting APS or
265 BLIPS risk criteria also met the mentioned item of the URC, but not vice versa).
266 Despite the lower specificity of these symptoms, we have recently shown that by including
267 the URC the BSIP ensures not to miss any referred individual at-risk who later transitioned to
268 frank psychosis (sensitivity of 1) at the cost of identifying more false positives (specificity of
269 0.35) (Papmeyer et al., 2017). As shown in this study, among the patients included in the
270 URC only category, 5% transitioned to psychosis, which is still not negligible considering that
271 otherwise these patients would not have been identified as at-risk patients.
272 Major strengths of the study are the long period of follow up compared to many of the UHR
273 studies so that transitions could be seen up to seven years after initial assessment and the
274 big sample size. The main limitation of the study is that the results shown provide the
275 predictive performance of a certain risk category in comparison to others with a somehow
276 artificial distinction of risk groups to avoid overlap of different categories.
277 In conclusion, our results support the need for a more exact distinction of the components of
278 the ARMS construct with different classes of risk guiding more specific interventions.
279 Integrating the URC into the clinical staging model for psychotic and severe mood disorders
280 as proposed by McGorry, Hickie, Yung, Pantelis, and Jackson (2006), we could assimilate
281 this subgroup to the stage 1a (mild or non-specific symptoms). This stage represents a lower
Unspecific risk for psychosis

282 grade of psychopathology compared to patients who meet the UHR criteria (stage 1b). The
283 access to low-stigma services with psychoeducation, monitoring and low threshold
284 interventions (e.g., substance abuse reduction, cognitive behavioral therapy) addressing the
285 full range of early psychopathology and according to the individuals needs may be a useful
286 strategy for these patients.

287 **Acknowledgements:**

288 We thank our colleagues from the Center for Gender Research and Early Detection who
289 provided insight and expertise that greatly assisted the elaboration of different versions of
290 this paper.

291 **Conflicts of interest:**

292 All authors declare to have no conflicts of interest regarding the content of this article.

293

294

295 REFERENCES

- 296 American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental*
 297 *disorders : DSM-III-R* (3rd ed.). Washington, DC: American Psychiatric Association.
 298 Andreasen, N. C. (1989). The Scale for the Assessment of Negative Symptoms (SANS):
 299 conceptual and theoretical foundations. *Br J Psychiatry Suppl(7)*, 49-58.
 300 Aston, J., Bull, N., Gschwandtner, U., Pflueger, M., Borgwardt, S., Stieglitz, R. D., & Riecher-
 301 Rössler, A. (2012). First self-perceived signs and symptoms in emerging psychosis
 302 compared with depression. *Early Interv Psychiatry*, 6(4), 455-459.
 303 Cannon, Changhong Yu, Jean Addington, Carrie E. Bearden, Kristin S. Cadenhead, Barbara
 304 A. Cornblatt, . . . Michael W. Kattan. (2016). An individualized risk calculator for
 305 research in prodromal psychosis. *Am J Psychiatry*, 173(10), 980-988.
 306 Carrion, R. E., Correll, C. U., Auther, A. M., & Cornblatt, B. A. (2017). A Severity-Based
 307 Clinical staging model for the psychosis prodrome: Longitudinal findings from the
 308 New York recognition and prevention program. *Schizophr Bull*, 43(1), 64-74.
 309 Cornblatt, B. A., & Carrion, R. E. (2016). Deconstructing the psychosis risk syndrome:
 310 moving the field of prevention forward. *JAMA Psychiatry*, 73(2), 105-106.
 311 Cuesta, M. J., & Peralta, V. (2008). Current psychopathological issues in psychosis: towards a
 312 phenotype-wide scanning approach. *Schizophr Bull*, 34(4), 587-590.
 313 Dazzi, F., Shafer, A., & Lauriola, M. (2016). Meta-analysis of the Brief Psychiatric Rating
 314 Scale - Expanded (BPRS-E) structure and arguments for a new version. *J Psychiatr
 315 Res*, 81, 140-151.
 316 Fusar-Poli, P. (2017). The clinical high-risk state for psychosis (CHR-P), Version II.
 317 *Schizophr Bull*, 43(1), 44-47.
 318 Fusar-Poli, P., Bonoldi, I., Yung, A. R., & et al. (2012). Predicting psychosis: Meta-analysis of
 319 transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry*, 69(3),
 320 220-229.
 321 Fusar-Poli, P., Borgwardt, S., Bechdolf, A., & et al. (2013). The psychosis high-risk state: A
 322 comprehensive state-of-the-art review. *JAMA Psychiatry*, 70(1), 107-120.
 323 Fusar-Poli, P., Cappucciati, M., Borgwardt, S., Woods, S. W., Addington, J., Nelson, B., . . .
 324 McGuire, P. K. (2016). Heterogeneity of psychosis risk within individuals at clinical
 325 high risk: a meta-analytical stratification. *JAMA Psychiatry*, 73(2), 113-120.
 326 Fusar-Poli, P., Cappucciati, M., Rutigliano, G., Schultze-Lutter, F., Bonoldi, I., Borgwardt, S.,
 327 . . . McGuire, P. (2015). At risk or not at risk? A meta-analysis of the prognostic
 328 accuracy of psychometric interviews for psychosis prediction. *World Psychiatry*,
 329 14(3), 322-332.
 330 Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A. R., & McGuire, P. K. (2014). Comorbid
 331 depressive and anxiety disorders in 509 individuals with an at-risk mental state:
 332 impact on psychopathology and transition to psychosis. *Schizophr Bull*, 40(1), 120-
 333 131.
 334 Häfner, H., Maurer, K., Löffler, W., an der Heiden, W., Munk-Jorgensen, P., Hambrecht, M.,
 335 & Riecher-Rössler, A. (1998). The ABC schizophrenia study: a preliminary overview of
 336 the results. *Soc Psychiatry Psychiatr Epidemiol*, 33(8), 380-386.
 337 Häfner, H., Riecher-Rössler, A., Hambrecht, M., Maurer, K., Meissner, S., Schmidtke, A., . . .
 338 van der Heiden, W. (1992). IRAOS: an instrument for the assessment of onset and
 339 early course of schizophrenia. *Schizophr Res*, 6(3), 209-223.
 340 Häfner, H., Riecher-Rössler, A., Maurer, K., Fätkenheuer, B., & Löffler, W. (1992). First onset
 341 and early symptomatology of schizophrenia. A chapter of epidemiological and
 342 neurobiological research into age and sex differences. *Eur Arch Psychiatry Clin
 343 Neurosci*, 242(2-3), 109-118.
 344 Horneland, M., Vaglum, P., & Larsen, T. K. (2002). The prevalence of DSM-III-R
 345 "prodromal" symptoms of schizophrenia in non-psychotic psychiatric outpatients.
 346 *Nord J Psychiatry*, 56(4), 247-251.
 347 Jackson, H. J., McGorry, P. D., & Dudgeon, P. (1995). Prodromal symptoms of schizophrenia
 348 in first-episode psychosis: Prevalence and specificity. *Compr Psychiatry*, 36(4), 241-
 349 250.

- 350 Klosterkötter, J., Hellmich, M., Steinmeyer, E. M., & Schultze-Lutter, F. (2001). Diagnosing
 351 schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry*, 58(2), 158-164.
 352 McGorry, Hickie, I. B., Yung, A. R., Pantelis, C., & Jackson, H. J. (2006). Clinical staging of
 353 psychiatric disorders: a heuristic framework for choosing earlier, safer and more
 354 effective interventions. *Aust N Z J Psychiatry*, 40(8), 616-622.
 355 McGorry, & Nelson, B. (2016). Why we need a transdiagnostic staging approach to emerging
 356 psychopathology, early diagnosis, and treatment. *JAMA Psychiatry*, 73(3), 191-192.
 357 McGorry, Nelson, B., Amminger, G. P., Bechdolf, A., Francey, S. M., Berger, G., ... Yung, A.
 358 R. (2009). Intervention in individuals at ultra-high risk for psychosis: a review and
 359 future directions. *J Clin Psychiatry*, 70(9), 1206-1212.
 360 Müller, M., Vetter, S., Buchli-Kammermann, J., Stieglitz, R.-D., Stettbacher, A., & Riecher-
 361 Rössler, A. (2010). the self-screen-prodrome as a short screening tool for pre-
 362 psychotic states. *Schizophr Res*, 123(2), 217-224.
 363 Papmeyer, M., Aston, J., Everts-Graber, J., Heitz, U., Studerus, E., Borgwardt, S. J., ...
 364 Riecher-Rössler, A. (2017). Outcome of individuals "not at risk of psychosis" and
 365 prognostic accuracy of the Basel Screening Instrument for Psychosis (BSIP). *Early
 366 Interv Psychiatry*.
 367 R Development Core Team. (2017). R: A language and environment for statistical computing:
 368 R Foundation for Statistical Computing, Vienna, Austria. Retrieved from
 369 <https://www.R-project.org/>
 370 Riecher-Rössler, Aston, J., Borgwardt, S., Bugra, H., Fuhr, P., Gschwandtner, U., ...
 371 Zimmermann, R. (2013). [Prediction of Psychosis by Stepwise Multilevel Assessment
 372 – The Basel FePsy (Early Recognition of Psychosis)-Project]. *Fortschr Neurol
 373 Psychiatr*, 81(05), 265-275.
 374 Riecher-Rössler, Gschwandtner, U., Aston, J., Borgwardt, S., Drewe, M., Fuhr, P., ...
 375 Stieglitz, R. D. (2007). The Basel early-detection-of-psychosis (FEPSY)-study – design
 376 and preliminary results. *Acta Psych Scand*, 115(2), 114-125.
 377 Riecher-Rössler, Pflueger, M. O., Aston, J., Borgwardt, S. J., Brewer, W. J., Gschwandtner,
 378 U., & Stieglitz, R.-D. (2009). Efficacy of using cognitive status in predicting psychosis:
 379 A 7-year follow-up. *Biol Psychiatry*, 66(11), 1023-1030.
 380 Riecher-Rössler, & Studerus, E. (2017). Prediction of conversion to psychosis in individuals
 381 with an at-risk mental state: a brief update on recent developments. *Curr Op
 382 Psychiatry*, 30(3), 209-219.
 383 Riecher-Rössler, A., Aston, J., Ventura, J., Merlo, M., Borgwardt, S., Gschwandtner, U., &
 384 Stieglitz, R. D. (2008). [The Basel Screening Instrument for Psychosis (BSIP):
 385 development, structure, reliability and validity]. *Fortschr Neurol Psychiatr*, 76(4),
 386 207-216.
 387 Riecher-Rössler, A., Gschwandtner, U., Borgwardt, S., Aston, J., Pflueger, M., & Rössler, W.
 388 (2006). Early detection and treatment of schizophrenia: how early? *Acta Psychiatr
 389 Scand Suppl*(429), 73-80.
 390 Riecher-Rössler, A., McGorry, P. D., & Sartorius, N. (2016). *Early detection and intervention
 391 in psychosis state of the art and future perspectives*. Key Issues in Mental Health Vol.
 392 181. Karger, Basel.
 393 Schultze-Lutter, Michel, C., Schmidt, S. J., Schimmelmann, B. G., Maric, N. P., Salokangas,
 394 R. K., ... Klosterkötter, J. (2015). EPA guidance on the early detection of clinical high
 395 risk states of psychoses. *Eur Psychiatry*, 30(3), 405-416.
 396 Schultze-Lutter, F., Ruhrmann, S., Berning, J., Maier, W., & Klosterkötter, J. (2010). Basic
 397 symptoms and ultrahigh risk criteria: symptom development in the initial prodromal
 398 state. *Schizophr Bull*, 36(1), 182-191.
 399 van der Net, J. B., Janssens, A. C., Eijkemans, M. J., Kastelein, J. J., Sijbrands, E. J., &
 400 Steyerberg, E. W. (2008). Cox proportional hazards models have more statistical
 401 power than logistic regression models in cross-sectional genetic association studies.
 402 *Eur J Hum Genet*, 16(9), 1111-1116.
 403 van Os, J., & Guloksuz, S. (2017). A critique of the "ultra-high risk" and "transition"
 404 paradigm. *World Psychiatry*, 16(2), 200-206.

- 405 Ventura, J., Lukoff, D., Nuechterlein, K. H., Liberman, R. P., Green, M., & Shaner, A. (1993).
406 Training and quality assurance with the brief psychiatric rating scale: "The Drift
407 Busters"; Appendix 1. The Brief Psychiatric Rating Scale (expanded version). *Int J*
408 *Methods Psychiatric Res*, 3, 221-224.
409 Yung, A. R., Phillips, L. J., McGorry, P. D., McFarlane, C. A., Francey, S., Harrigan, S., . . .
410 Jackson, H. J. (1998). Prediction of psychosis. A step towards indicated prevention of
411 schizophrenia. *Br J Psychiatry Suppl*, 172(33), 14-20.
- 412
- 413
- 414
- 415
- 416
- 417
- 418
- 419
- 420
- 421
- 422
- 423

424 **Table 1:** Socio-demographic and clinical characteristics of the sample

425

	All N=200	ARMS-NT [†] N=156	ARMS-T N=44	Hazard Ratio [95% CI]	p-value
Gender:					
Women	62 (31.0%)	44 (28.2%)	18 (40.9%)	Ref.	
Men	138 (69.0%)	112 (71.8%)	26 (59.1%)	0.67 [0.37;1.23]	0.194
Age	25.1 (6.9)	24.9 (7.0)	25.8 (6.5)	1.00 [0.97;1.04]	0.818
Years of education	11.7 (2.8)	11.9 (2.9)	11.1 (2.4)	0.90 [0.81;1.01]	0.079°
BPRS Activation	3.8 (1.5)	3.8 (1.5)	3.9 (1.7)	1.06 [0.89;1.27]	0.501
BPRS Positive Symptoms	5.5 (2.1)	5.3 (2.1)	6.3 (2.0)	1.24 [1.09;1.42]	0.001***
BPRS Negative Symptoms	5.5 (2.7)	5.4 (2.6)	5.7 (2.9)	0.99 [0.89;1.11]	0.888
BPRS Affect	6.8 (2.8)	6.7 (2.9)	7.0 (2.7)	1.03 [0.93;1.14]	0.590
BPRS Disorganization	3.9 (1.3)	3.8 (1.2)	4.4 (1.7)	1.27 [1.05;1.52]	0.011*
BPRS total score	39.3 (8.8)	38.6 (8.5)	41.8 (9.4)	1.03 [1.00;1.07]	0.037*
SANS total score	21.5 (16.1)	20.6 (16.3)	24.7 (15.0)	1.01 [0.99;1.03]	0.269

For gender, absolute numbers with percentages in parenthesis are reported. For all other variables means with standard deviations in parenthesis are reported. ARMS-NT = at-risk mental state without later transition to psychosis; ARMS-T = at-risk mental state with later transition to psychosis; CI = confidence interval; BPRS = Brief Psychiatric Rating Scale (Ventura et al., 1993); SANS = Scale for the Assessment of Negative Symptoms (Andreasen, 1989).

° p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001[†] 66 of these patients had a follow-up duration of less than 2 years and hence can only be tentatively called ARMS-NT patients. However, since associations with later transition to psychosis were tested with survival analyses, which can accommodate for short follow-up durations, significance estimates should still be accurate.

426

427

428

429

430

431

432

433

434

435

436

Table 2: Psychosis risk comparison for different risk categories using survival analysis.

	All N=200	ARMS-NT [†] N=156	ARMS-T N=44	Hazard Ratio [95% CI]	p-value
Risk group:					
BLIPS	15 (7.5%)	11 (7.1%)	4 (9.1%)	4.93 [0.90;27.0] [‡]	0.066 [°]
APS, but not BLIPS	128 (64.0%)	90 (57.7%)	38 (86.4%)	5.84 [1.41;24.2] [‡]	0.015*
GRD, but not APS or BLIPS	17 (8.5%)	17 (10.9%)	0 (0.0%)	0.00 [0.00; [‡]]	0.997
URC only	40 (20.0%)	38 (24.4%)	2 (4.5%)	0.19 [0.05;0.80] [§]	0.024*

ARMS-NT = at-risk mental state without later transition to psychosis; ARMS-T = at-risk mental state with later transition to psychosis; CI = confidence interval; APS = attenuated psychotic symptoms; BLIPS = brief limited intermittent psychotic symptoms; GRD = genetic risk and deterioration syndrome; URC = unspecific risk category.

[°] p < 0.1, * p < 0.05[†] 66 of these patients had a follow-up duration of less than 2 years and hence can only be tentatively called ARMS-NT patients. However, since associations with later transition to psychosis were tested with survival analyses, which can accommodate for short follow-up durations, significance estimates should still be accurate.

[‡] When compared to the URC only group

[§] When compared to all other risk groups combined

439 **Table 3:** Predictive values of items comprised in the URC criterion of the BSIP in the total
 440 sample
 441

	ARMS-NT [†] N=156	ARMS-T N=44	Hazard Ratio [95% CI]	p-value	N [‡]
Male < 25 years or female < 30 years	10 (69.2%)	27 (61.4%)	0.78 [0.42;1.43]	0.421	200
Social isolation	82 (52.9%)	24 (57.1%)	1.29 [0.70;2.39]	0.411	197
Impaired role functioning	107 (69.9)	32 (74.4%)	1.29 [0.65;2.56]	0.468	196
Peculiar behavior [§]	20 (12.9%)	3 (7.0%)	0.54 [0.17;1.75]	0.304	198
Impairment in personal hygiene	23 (14.9%)	10 (23.3%)	1.69 [0.83;3.44]	0.145	197
Blunted or inappropriate affect	73 (49.0%)	20 (48.8%)	1.15 [0.62;2.12]	0.665	190
Disturbances of speech [§]	29 (18.8%)	8 (19.5%)	1.04 [0.48;2.26]	0.917	195
Odd beliefs [§]	45 (29.2%)	21 (48.8%)	1.78 [0.97;3.24]	0.061°	197
Unusual perceptual experiences [§]	60 (39.5%)	21 (48.8%)	1.28 [0.70;2.32]	0.425	195
Lack of initiative	108 (69.7)	32 (78.0%)	1.59 [0.76;3.34]	0.223	196
Other unspecific prodromal signs	135 (86.5)	34 (79.1%)	0.72 [0.35;1.50]	0.382	199
Ever experienced psychotic or attenuated psychotic symptoms [§]	109 (69.9)	42 (95.5%)	6.70 [1.62;27.7]	0.009**	200
Social decline [§]	112 (73.2)	31 (72.1%)	1.05 [0.54;2.05]	0.878	196
Drug use (regularly in the last 2 years)	67 (43.2%)	21 (48.8%)	1.41 [0.78;2.57]	0.258	198
Previous psychiatric disease	96 (62.7%)	20 (47.6%)	0.62 [0.34;1.13]	0.119	195
Suspected or confirmed psychosis in first-degree relative	24 (18.2%)	8 (19.5%)	1.02 [0.47;2.22]	0.954	173
Confirmed psychosis in second-degree relative	24 (18.5%)	3 (7.3%)	0.44 [0.13;1.42]	0.168	171
Referral with suspected psychosis	95 (79.8%)	18 (66.7%)	0.63 [0.28;1.41]	0.262	146

BSIP = Basel Screening Instrument for Psychosis; ARMS-NT = at-risk mental state without later transition to psychosis; ARMS-T = at-risk mental state with later transition to psychosis; CI = confidence interval; APS = attenuated psychotic symptoms; BLIPS = brief limited intermittent psychotic symptoms; URC = unspecific risk category.

° p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

† 66 of these patients had a follow-up duration of less than 2 years and hence can only be tentatively called ARMS-NT patients. However, since associations with later transition to psychosis were tested with survival analyses, which can accommodate for short follow-up durations, significance estimates should still be accurate.

‡ Number of cases with non-missing information

§ Highly specific items according to the BSIP.

442

443

444 **FIGURE LEGENDS**

445 **Figure 1.** Venn diagram showing number of cases fulfilling criteria for attenuated psychotic
446 symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), genetic
447 risk and deterioration syndrome (GRD) and the unspecific risk category (URC) at
448 baseline assessment.

449 **Figure 2.** Kaplan-Meier estimates of proportions of individuals remaining non-psychotic over
450 time stratified for different risk criteria.