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Verfügung
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Sehr geehrter Herr Prof. Schimmelmann

Wir freuen uns, Ihnen mitzuteilen, dass der Forschungsrat beschlossen hat, für das Projekt "Früherkennung von Psychosen im Kindes- und Jugendalter: Evaluation der Risikokriterien" einen Forschungsbeitrag von CHF 291'191.00 zuzusprechen. Weitere Angaben zur Beurteilung Ihres Gesuches finden Sie direkt in mySNF.

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Für die Realisierung Ihres Vorhabens wünschen wir Ihnen viel Erfolg.

Freundliche Grüsse

i.V.

Dr. Ayşim Yılmaz

Aufteilung der Zusprache nach Rubriken

	Total	1. Tranche	2. Tranche	3. Tranche
Projekt				
Apparate	0	0	0	0
Forschungsmittel	25'767	6'687	8'350	10'730
Saläre	223'044	71'608	74'690	76'746
Sozialabgaben	42'380	42'380	0	0
Total	291'191	120'675	83'040	87'476

Beginn: 1. Januar 2013 Dauer: 36 Monate

Bedingungen

Saläre: Bewilligt:
N.N., Postdoc, 50%, 36 Monate
CHF 35'804.- / 37'345.- / 38'373.-
N.N., Postdoc, 50%, 36 Monate
CHF 35'804.- / 37'345.- / 38'373.-

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Zum Projekt gehören als weitere Beitragsempfängerinnen und Beitragsempfänger:

- Dr. Frauke Schultze-Lutter, Universitätsklinik für Kinder- und Jugendpsychiatrie Universitäre Psychiatrische Dienste Bern, 3000 Bern 60 UPD
- Prof. Gerd Lehmkuhl, Klinik und Poliklinik für Kinder- und Jugendpsychiatrie der Universität zu Köln, 50931 Köln

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Relevante Rechtsdokumente
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Insbesondere:

- Beitragsreglement
- Allgemeines Ausführungsreglement zum Beitragsreglement
- Reglement über die Information, die Valorisierung und die Rechte an den Forschungsresultaten

Rechtsmittelbelehrung

Gegen diese Verfügung kann gemäss Art. 13 des Bundesgesetzes vom 7. Oktober 1983 über die Förderung der Forschung und der Innovation (SR 420.1) innerhalb von 30 Tagen nach Eröffnung Beschwerde beim Bundesverwaltungsgericht, Postfach, 9023 St. Gallen, eingereicht werden.

Die Beschwerdeschrift hat die Begehren, deren Begründung mit Angabe der Beweismittel und die Unterschrift der Beschwerdeführerin bzw. des Beschwerdeführers oder der Vertreterin bzw. des Vertreters zu enthalten.

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0. Responsible Applicant: Prof. Dr. med. Benno G. Schimmelmann

Title of Project: Early detection of psychosis in children and adolescents: An evaluation of current at-risk criteria

Background: Psychoses have an incidence of about 3% with a peak of first onset around the age of 20; 10 to 15% have an onset before the age of 18. These 'early-onset psychoses' (EOP) are generally considered to have an even poorer prognosis than 'adult-onset psychoses' (AOP) that have repeatedly been shown to cause enormous disability and costs. Currently, an early detection of and intervention in persons with first signs of emerging psychosis is regarded a promising strategy to reduce the burden of this disease. To this aim, two complementary sets of at-risk criteria have been developed on mainly adult samples: (1) 'ultra high risk' criteria (**UHR**) including attenuated and brief limited intermittent psychotic symptoms and a combination of a genetic risk factor and a recent significant functional decline and (2) the basic symptom criteria (**BS**) 'cognitive-perceptive basic symptoms' and 'cognitive disturbances'. To date, prevention research in psychosis has mainly been carried out in adult or mixed-age help-seeking at-risk samples, i.e., including a small fraction of mainly older adolescents. And despite some indications that at-risk criteria perform differently in adolescent samples – not least due to developmental aspects, no study has hitherto systematically examined the clinical validity and predictive value of at-risk criteria or of the currently discussed additional neuropsychological predictors of psychosis in child and adolescent (CAD) samples.

Working hypothesis and specific aims: The primary aim is to examine the conversion rate to frank psychosis in an at-risk CAD sample (**AtRisk**) and thereby the *positive predictive power* of at-risk criteria. Based on the literature, we expect a lower first-year conversion rate compared to adults (<20%), while the second-year conversion rate (no change, increase or decrease compared the first-year) is unclear. The seven secondary aims are: (1) to assess the prevalence rates of at-risk criteria, and sociodemographic and neuropsychological predictors, proposed to enhance predictive accuracy, and to identify the main predictors of conversion to psychosis in AtRisk. We expect a different set of predictors compared to adults; (2) to explore the risk enhancing properties of genetic polymorphisms; (3) to examine the risk enhancing properties of functional imaging data (in a subsample); (4) to assess the general outcome of AtRisk beyond conversion to psychosis and the role of life events in this; (5) to assess the prevalence of at-risk criteria prior to the onset of psychotic symptoms (in the prodromal phase) in a first admitted **EOP** sample and thereby the *sensitivity* of at-risk criteria in CAD. We expect an equal or higher sensitivity in EOP compared to AOP; (6) to assess prevalence rates and distributions of at-risk criteria and additional potential predictors of conversion to psychosis in a general population (**GPS**) as well as a clinical non-psychotic sample (**ClinS**) with diagnoses, for which an increased prevalence of subsequent psychosis were reported, allowing for calculation of *negative predictive power* and *specificity* estimates; and (7) to explore gender differences in the frequency and distribution of at-risk criteria.

Methods: This is a prospective multi-centre naturalistic 3-year follow-up study (Bern, Zurich, Cologne) on altogether 209 AtRisk, 264 ClinS, 250 GPS and 100 EOP. At-risk symptoms and criteria will be assessed with the 'Structured Interview for Prodromal Syndromes' and the 'Schizophrenia Prediction Instrument, Child & Youth version'. Further, sociodemographics and functioning measures, DSM-IV diagnoses as well as potential neuropsychological predictors of conversion (verbal fluency, verbal and working memory as well as processing speed) will be assessed. AtRisk and ClinS will be recruited over 2 years and followed annually at year 1 and 2, GPS will be recruited in year 1 and followed annually at year 1 and 2. Beyond the funded study period, all participating centres have agreed to further follow-up AtRisk until 5-year follow-up as in-house contributions. Repeated collection of saliva samples will allow genetic/epigenetic analyses.

Expected value: Our study will be the first to examine the validity of current at-risk criteria as well as of proposed measures to enhance their accuracy (e.g., neuropsychology, genetics) in CAD and to provide starting points for their potential revision. With more and more CAD psychiatrists taking an interest in early detection and intervention in psychosis, the results of the proposed project will be received with immense interest by the international research community. The impact of the proposed study on future early detection research will vary depending on its results: If the sensitivity of 'fulfilling any current at-risk criterion' is low, especially in EOP, a completely different or additional set of at-risk criteria for CAD is needed. A more or less comprehensive revision of at-risk criteria for CAD, however, is needed, (i) if the positive predictive power of at-risk criteria is low in AtRisk, (ii) if their specificity and negative predictive power are low in ClinS and GPS and/or (iii) if their prevalence in GPS is high. Such revisions may include the addition of predictors, the elimination of single criteria and/or their redefinition in terms of frequency- and/or time-criteria. Overall, the study's practical and potential economic impact will be considerable especially in light of the current discussion about the role of at-risk criteria in DSM-5 and the potential for further neurobiological research on this phenotype.

2. Scientific Program

2.1. Background

Four of the six leading causes of the years lived with disability (YLD) are due to neuropsychiatric disorders - one of them is schizophrenia (WHO 2004). The devastating consequences are aggravated when the disorder has an early onset before the age of 18 - because, amongst others, its detection appears to be even more delayed than in the adult-onset form (Schimmelmann et al. 2007a). To date, an early detection and prevention is considered an essential strategy to avoid YLD, reduce the stigma, increase considerably the social capital, help reduce poverty and promote a country's development (WHO 2004). Yet, potential developmental or age-related particularities in the early detection of psychoses in **children and adolescents** (**CAD**) have hitherto not been studied (Schultze-Lutter et al. 2011; Schimmelmann & Schultze-Lutter 2012).

2.1.1. Early detection of psychoses

The major peak of first-episode psychosis onset is in late adolescence and early adulthood (Kirkbride et al. 2006); 15% of this group are **early-onset psychoses** (**EOP;** onset before age 18) while very early-onset psychoses (onset before age 13) are rare. In the vast majority of cases, the 1st episode is preceded by a prodrome of 5 to 6 years on average, in which a multitude of mental problems, symptoms and first psychosocial deficits occur (Häfner et al. 1995; Schultze-Lutter et al. 2010). Moreover, a longer duration of untreated psychosis, DUP, and of untreated illness incl. the prodrome, DUI, has been related to more negative outcome (Marshall et al. 2005; Schimmelmann et al. 2008). In a comparison of the course of EOP and **adult-onset psychoses** (**AOP**), a significantly longer DUP in EOP accounted for their worse course after controlling for type of psychosis, premorbid functioning, family support and psychiatric history (Schimmelmann et al. 2007a). Hence the **negative effects of DUI/DUP** may even be **aggravated in EOP**, possibly because more pronounced neurodevelopmental and cognitive deficits, the insidious onset of less pronounced positive symptoms or the atypical clinical picture of the beginning EOP – possibly misinterpreted as 'adolescent crisis' – act as further delaying factors (ibid.). Thus, **early detection and treatment** of persons with first signs of the emerging disorder, which is currently regarded as a promising strategy in fighting the devastating consequences of psychosis, **may face different or additional challenges in EOP as compared to AOP**.

For an early detection of psychoses, two complementary approaches (*Appendix 1*) are mainly followed: (1) the **'ultra high risk' (UHR) criteria** of an imminent risk including attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) and a combination of a genetic risk factor and a recent persistent significant decline in functioning (Phillips et al. 2000) and (2) the **basic symptom (BS) criteria** 'cognitive-perceptive basic symptoms' (COPER; Klosterkötter et al. 2001) and 'cognitive disturbances' (COGDIS; Schultze-Lutter et al. 2006,2007a,b). These at-risk criteria, however, were developed solely (Klosterkötter et al. 2001) or predominately in adult samples (age 16 and above; Phillips et al. 2000).

First studies of these criteria – in predominately adult samples – have shown conversion rates in thus defined, help-seeking clinical at-risk samples that by far exceed the general incidence of first-episode psychosis of about 0.03% (Baldwin et al. 2005): the annual conversion rate for not specifically or untreated UHR samples is about 20% on average, and about 25% in samples meeting BS criteria (Schultze-Lutter et al. 2011). While at-risk patients most frequently present with more than one of these five risk criteria (Schultze-Lutter et al. 2009; Ruhrmann et al. 2011), there is first evidence that particularly the combination of APS and COGDIS might further improve detection of imminent risk for psychosis (Ruhrmann et al. 2011; Schultze-Lutter et al. 2012).

Two large longitudinal studies (Cannon et al. 2008; Ruhrmann et al. 2011) have as yet reported regression equations and prognostic scores respectively based on sociodemographic and clinical variables, which allow more detailed risk estimation in at-risk samples. These include: the total of positive syndrome (P-)items of the Structured Interview for Prodromal Syndromes (SIPS), its single P-items 'unusual thought content' and 'suspiciousness', schizotypal personality, 'bizarre thought content' and 'sleep disturbances' according to the SIPS, current social functioning, highest level of global functioning within the pre-baseline year, years of education and presence of any drug abuse (ibid.).

Additionally, in several longitudinal comparisons of at-risk subjects with and without conversion to psychosis, **certain neuropsychological parameters** (esp. verbal fluency, processing speed, verbal and working memory) **consistently** appeared as **promising candidates** to further improve prediction (Pukrop & Klosterkötter 2010). Level of stress and stressful life events moderate the course in at-risk persons (Phillips 2005; Tessner et al. 2011). Initial evidence suggests that neuroimaging (Michelli et al. 2011; Koutsouleris et al. 2009) and genetic (Keri et al. 2009; Mössner et al. 2010) parameters may also improve prediction in adults. Studies on other potentially risk enhancing parameters as yet either relate to rather small subsamples of converters to psychosis or have resulted in contradictory results (overview in: Schultze-Lutter & Ruhrmann 2008).

2.1.2. Early detection of psychoses in CAD

While these are promising **results** in general, first reports on CAD meeting at-risk criteria indicate that these might **not be unrestricted transferable to this young age group** (Schultze-Lutter et al. 2011). As for UHR criteria, two available longitudinal naturalistic studies on small samples of adolescents with APS (N=48; Cornblatt et al. 2007) and UHR or COGDIS (N=58; Ziermans et al. 2011) reported contradicting results: while Cornblatt et al. (2007) reported a more insidious onset of frank psychoses (longer interval between study intake and conversion) than reported from adult or mixed samples, the conversion rate reported by Ziermans et al. (2011) was slightly lower (16% within 2 years) but the timing was comparable to that of adults. Further, the predictive value of the highly frequent APS 'suspiciousness, persecutory ideas' was questioned in this age group (Cornblatt et al. 2007). Contrariwise, Meyer et al. (2005) reported this particular APS at an only moderate incidence rate in an adolescent at-risk sample while the most frequent APS were 'perceptual abnormalities' and non-paranoid 'unusual thought content, delusional ideas'. Thus, the **prevalence and predictive value of APS in CAD in at-risk samples are hitherto unclear.**

This is **also true for BLIPS**: Children's reports about psychotic experiences are difficult to clinically classify when observable behavioural correlates are missing, thus probably leading to an overestimation of psychotic symptoms in children in structured interviews (Hlastala & McClellan 2005). Atypical psychotic symptoms, which could well meet BLIPS criteria, were reported to be relatively frequent in CAD (ibid.; Bartels-Velthuis et al. 2011). They often occurred with other mental disorders, were fleeting and/or closely context-related experiences, in most cases remitted completely, and had hardly any relation to conversion to psychosis (ibid.). Thus, contrary to adult samples, atypical or transient psychotic symptoms may not qualify as predictors of psychosis in CAD samples. Contrary to this, a birth cohort study (Poulton et al. 2000) reported a high predictive validity of psychotic symptoms reported at age 11 for a schizophreniform or – though less so – an anxiety disorder at age 24.

As for **BS criteria**, **few data on their predictive value in CAD samples** is as yet available (Schultze-Lutter et al. 2011). In the study of Ziermans et al. (2011), 21% of the subgroup of adolescents with COGDIS (n=39) developed a psychotic disorder within 2 years, mainly within the first year.

As regards the **prevalence of at-risk criteria and phenomena in the general population**, in CAD as well as adults, only preliminary data exists. In CAD, a **recent study restricted to** 212 **11- to 13-year olds**, reported the prevalence of **UHR** at-risk criteria at 8.1% (Kelleher et al. 2011). The preliminary results of our **own epidemiological study on predominately adults** (16- to 40-year olds; so far, 96% of 758 interviewees were 18 years and above) and our related pilot study (Schimmelmann et al. 2011a) showed a prevalence of UHR criteria of only 0.1% (n=1) and 2% (n=1; notably occurring in a 16-year old). These findings indicate **that UHR at-risk criteria and phenomena might be more frequent and possess lesser psychopathological meaning in CAD compared to young adults**.

Despite the indications that early detection of psychoses need to be specifically addressed in CAD, **in present early detection and early intervention studies,** the **focus on adult or mixed help-seeking at-risk persons** is **continued** such as in the 5th work package of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (**EU-GEI**; EC's 7th Framework Program; EU-GEI 2008), the North American Prodrome Longitudinal Study (**NAPLS**; Addington et al. 2007), or the Secondary Prevention of Schizophrenia (**PREVENT**) that is funded by the German Research Foundation (DFG) and compares psychological to pharmacological treatment in adult at-risk persons. Another large-scale study with participation of Swiss sites (Basel, Winterthur), the North America, Europe, Australia Prodrome Study (**NEURA-PRO**; McGorry et al. 2009), is funded by a grant from the Stanley Medical Research Institute and examines the efficacy of a neuroprotective intervention in a mixed at-risk sample. In Switzerland, early detection and related basic research on the development of psychosis in adolescent and adult at-risk persons are studied within the **Bruderholz** Study (e.g. Simon et al. 2006) initially funded by a grant of the Freiwillige Akademische Gesellschaft Basel, in adults within the framework of the Früherkennung von Psychosen study (**FEPSY**; e.g. Gschwandtner et al. 2003) supported by the Swiss National Foundation (SNF No. PBBS33-106936, 3200-057216 and 32323B-119382) as well as within early detection and intervention projects on adult persons associated with the University of Lausanne (SNF No. PBLA33-119622 and 32003B-112160) and Basel (SNF No. PBBS1-104680). Early detection and treatment of psychotic and bipolar disorders is also one of seven projects of the Zürcher Impulsprogramm zur nachhaltigen Entwicklung in der Psychiatrie (**ZInEP**) in that also the Department of Child and Adolescent Psychiatry of the University of Zurich participates and with that a cooperation is implemented. Furthermore, our own SNF supported project (No. 32003B_135381), the epidemiological telephone study on the prevalence and burden of at-risk criteria in the general population, focuses mainly on adults.

2.1.3. Research gaps

In summary, research on early detection and intervention in psychosis has as yet been carried out in **predominately adult samples of help-seeking at-risk persons** without consideration of possible special requirements in CAD. At an average duration of the prodrome of 5-6 years, prodromal states of psychosis in late adolescence or early adulthood (i.e. the peak incidence of psychoses) should occur in CAD at a significant rate. And although reports indicate **particularities of at-risk criteria in CAD** such as a potential lack of clinical validity of BLIPS and certain APS (see 2.1.2.), these **have not as yet been systematically studied**. Hence neither the rate or timing of conversion to psychosis in CAD fulfilling current at-risk criteria nor the prevalence rates of at-risk criteria in clinical and general population samples are known – presumptions to estimate their predictive accuracy and to determine their pathologic nature. In addition, it has never been studied if these criteria occur in the prodromal phase of EOP at a frequency sufficient to allow the early detection of the majority of cases. Despite these gaps of knowledge, the current suggestion of an Attenuated Psychosis Syndrome modelled on APS and to be included in DSM-5 does not envision a cautionary statement for its use in CAD (http://www.dsm5.org/). Furthermore, it is unknown whether polymorphisms associated with psychosis or with conversion to psychosis in at-risk adults are relevant biomarkers predicting which CAD at high risk will subsequently develop psychosis. The risk enhancing potential of functional imaging data have only once been studied in adults (Allen et al. 2012) and not in CAD.

Thus, a **study of at-risk criteria in CAD** is **essential and clearly required** to examine if current criteria and the Attenuated Psychosis Syndrome operationalization need to be adapted to this age-group. The anticipated findings will be most important for developing effective preventive youth services on national and international level and to design translational aetiology-oriented studies on the development of psychosis in CAD.

2.2. Own Research

The main applicant **Benno Graf Schimmelmann (BGS)** was principal investigator in several multi-centre studies on EOP and AOP, to which he contributed his developmental perspective as a child and adolescent psychiatrist, e.g., the First Episode Psychosis Outcome Study (FEPOS; e.g., Schimmelmann et al. 2005,2006,2007a,2008, 2011b,c; Lambert et al. 2005a,b, 2010a; Conus et al. 2010), the 'Verbundstudie Schizophrene Psychose in der Adoleszenz' (Meng et al. 2006,2009, supported by SNF: 3200-056047), the Schizophrenia Health Outcome study (SOHO; e.g. Lambert et al. 2009; Karow et al. 2007) and the ACCESS study (Lambert et al. 2010b). In FEPOS examining differences between adolescent and young adult onset first episode psychosis (Schimmelmann et al. 2007a), a clearly longer duration of untreated psychosis was detected specifically in adolescent onset psychosis. It was concluded that **early detection of adolescent psychosis may require specific strategies** in order to reduce misdiagnosis and, thereby attenuate distress and disability in patients and their families related to the unacknowledged and thus not appropriately treated disorder. Further, to our knowledge, only VESPA (Meng et al. 2009) has hitherto assessed the prevalence of at-risk symptoms in a representative sample of 96 13- to 20-year-olds from the general population of Basel, i.e. symptoms included in COPER and COGDIS as part of a larger test battery for basic symptoms. It was concluded from cross-sectional comparisons of patients with EOP and other psychiatric disorders that particularly cognitive basic symptoms may be valuable risk criteria in adolescents. Further post-hoc analyses revealed a **6-month prevalence rate of COGDIS of 3.1% and COPER of 8.0% in the general population** sample; yet these numbers give only an upper approximation, because onset and severity criteria had not been assessed. A small epidemiological pilot study on the prevalence of at-risk criteria (UHR and BS criteria) carried out in autumn 2009 (Schimmelmann et al. 2011c) led to a large **epidemiological study funded by SNF grant 32003B_135381** to the co-applicant Schultze-Lutter and BGS (see also 2.1.2). For its design as a telephone study, this project focuses **predominately** on **adults** (age 16 to 40 years) and is **more restricted in its assessments**. Specifically, it takes not into account all symptoms assessed in the SIPS and SPI-CY, but only those included in at-risk criteria. **The assessment of these other symptoms is necessary as they might add important risk information in CAD**. Furthermore, relevant disorders in CAD, neuropsychological and genetic parameters, and life events are not considered in the telephone survey. Furthermore, BGS has conducted or participated in several genetic multi-centre studies (Friedel et al. 2005; Hinney et al. 2011; Schimmelmann et al. 2007b, 2009)

The co-applicant **Frauke Schultze-Lutter (FSL)** is an expert in the early detection and intervention in psychosis and has been awarded with the Gerd Huber-Award **for Research on the Prevention of Psychosis** for her work into BS in 2010 (Schultze-Lutter 2009). She was the main research fellow in the Cologne Early Recognition (CER) study (Klosterkötter & Schultze-Lutter 2001, Klosterkötter et al. 2001, Schultze-Lutter et al. 2006,2007c). While first analyses of the CER data had led to the formulation of the **risk criterion COPER** (Klosterkötter et al. 2001), further analyses conducted within the framework of the FSL's doctoral thesis resulted in the development of the **high risk criterion**

COGDIS (Schultze-Lutter 2001; *Appendix 1*) that complements the UHR criteria increasingly in current national and international studies and early detection and intervention services: e.g., in the Bruderholz-study by Andor Simon in that FSL initially acted as an advisor; in the EC-funded European Prediction of Psychosis Study (EPOS) led by the Cologne Centre (Ruhrmann et al. 2011); in the Outreach And Support In South London (OASIS) service (Fusar-Poli et al. 2008); in EU-GEI (work package 5); in NEURA-PRO and PREVENT; and in the early detection part of the ZInEP project in that FSL provides the rater training for the assessments of at-risk criteria.

Funded by a grant of the Koeln Fortune Program/Faculty of Medicine, University of Cologne (projects 8/2005, 27/2006) to FSL, a follow-up of clients of the Early Recognition and Intervention Centre for mental crises, FETZ, of the University Hospital Cologne between 1998 and 2003 who had not already presented with frank psychosis was recently concluded (Schultze-Lutter et al. 2008a,2009). Of the 247 former clients who could be recontacted and interviewed, 87 (35.2%) had developed a psychotic episode during the follow-up period; preliminary analyses supported findings from EPOS (Ruhrmann et al. 2011) of a superior performance of the combination of APS and COGDIS.

Within the framework of the Awareness Program (Schultze-Lutter et al. 2010; BMBF grant 01 GI 0235), the **combination of APS and COPER symptoms** proved **sufficiently sensitive** for an early detection of psychosis – at least in adults: In this retrospective study, 98% of a sample of 128 **first-episode psychosis** inpatients showed a prodromal phase of at least one month (5.9±7.1 years) with altogether **87%** reporting APS (71.1%) and/or cognitive-perceptive basic symptoms (78.9%) (Schultze-Lutter et al. 2010). Notably, only 27.6% of this sample had sought help for mental problems in the prodromal phase suggesting a selection bias in sensitivity estimates that are based on prospective studies of help-seeking prodromal patients that will likely occur in CAD samples, too.

Based on the CER study and, with FSL as co-PI, supported by a grant of the DFG (KI 970/3-1,2), a **new instrument for the economic and quantitative assessment of BS**, the Schizophrenia Proneness Instrument, Adult version (**SPI-A**, Schultze-Lutter et al. 2007a,2008b), was developed and evaluated (Schultze-Lutter et al. 2007b,d,2008c). The SPI-A, comprising of six dimensions, has meanwhile become the **standard instrument for the assessment of BS criteria in adults**. An examination of the SPI-A dimensions in a CAD sample, could not replicate the dimensional structure of the SPI-A (Schultze-Lutter et al. 2011,2012). Thus, a **Child and Youth version** of the Schizophrenia Proneness Instrument (**SPI-CY**; Schultze-Lutter & Koch, 2010; Schultze-Lutter et al. in press) was **developed**. While it comprises of a larger set of items grouped in only four dimensions, the at-risk criteria (COPER, COGDIS) remained unchanged.

In co-operation with **co-applicant Gerd Lehmkuhl (GL)**, a cross-sectional pilot **study of the SPI-CY** in an adolescent sample (15.9±1.5 years) of gender and age matched (i) at-risk, (ii) clinical control and (iii) general population control samples (each n=20) was conducted. Results indicated significant differences on all four SPI-CY subscales both between clinical and the non-clinical group as well as between the two clinical groups. Thereby, at-risk subjects, mainly defined by APS, generally scored highest (Walger & Schultze-Lutter 2009). In all groups, the SPI-CY was well received (ibid.). Furthermore, GL and BGS successfully worked together in genetic research (Hinney et al. 2011).

FSL joined **BGS's** research group in Bern in 2009. Her long-term research experience in early detection of psychosis and BGS's research results that CAD may have special needs in early detection led to the understanding that current at-risk criteria are not necessarily transferable to CAD and need rigorous study. The rationale and importance of this study have been acknowledged by the research community by the recent publication of an editorial and a review (Schimmelmann 2011d; Schultze-Lutter et al. 2011) and by a poster price at the biennial International Early Psychosis Association (IEPA) conference for the outline of the rationale of this study. BGS and FSL are now members of the Swiss Early Psychosis Project board and FSL of the International Early Psychosis Association (IEPA) board. To this study, FSL contributes her clinical and research expertise in at-risk assessments and BGS the developmental perspective. **GL** will contribute his knowledge in at-risk assessment and research (Adam & Lehmkuhl 2002), as he founded the first German early detection of psychosis service for CAD in Germany, as well as genetic research expertise. FSL & BGS have a well-established cooperation with co-applicant GL. FSL will continue to supervise the quality of assessments.

2.3. Experimental Design

2.3.1. Hypotheses & Specific Aims

At-risk criteria for the early detection in psychoses are based mainly on adult samples and currently simply transferred to CAD without any systematic validation. Some unsystematic reports, however, indicate that developmental aspects play a role in the prognostic accuracy at least of certain at-risk symptoms. Hence it is assumed that at-risk criteria – at least in parts – need to be revised and adapted to CAD.

Aims

Primary aim

The primary aim is to examine the **conversion rate to psychosis in an at-risk CAD sample (AtRisk)** identified by BS and/or UHR-criteria over a follow-up period of at least one year (i.e., estimate of *positive predictive power* defined as the rate of conversions in those fulfilling any at-risk criterion). In adults, a current, more conservative estimate assumes a first-year conversion rate of 20% with decreasing annual conversion rates in the following years. Available data on CAD are in parts contradictory: Cornblatt et al. (2007) reported a lower conversion rate of about 6% in the first year and 13% in the second year indicating a lower, yet increasing annual conversion rate, whereas Ziermans et al. (2011) reported decreasing annual conversion rates of 12% within the 1st and 4% within the 2nd year. **Thus, we expect a lower 1st-year conversion rate compared to adults (<20%), while the 2nd-year conversion rate (no change, increase or decrease compared the first-year) is unclear.**

Secondary aims

(1) We will (i) assess the **prevalence rates and distributions of at-risk criteria and potential sociodemographic and neuropsychological predictors** in AtRisk and (ii) identify the **main predictors of conversion** among these variables. In addition, the two reported regression equations of clinical and sociodemographic predictors, proposed to enhance risk assessment within at-risk samples (Cannon et al. 2008; Ruhrmann et al. 2011), will be tested. As some differences between adults and CAD have already been reported (*see 2.1.2.*), **we expect a different set of predictors of conversion from those in adults**, esp. with regard to single APS**.**

(2) We will assess the predictive power of genetic polymorphisms in CAD, which were associated with psychosis or with conversion to psychosis in at-risk adults according to up-to-date studies. Epigenetic changes in these polymorphisms assessed at baseline and follow-ups will be explored for their contribution to the understanding of the involved environmental processes (EU-GEI 2008). Family based genetic association studies in a subsample of AtRisk with available parental saliva samples will assess the association of polymorphisms with an at-risk state in selected candidate genes.

(3) In AtRisk recruited in Bern, we will evaluate the risk stratifying properties of regional brain activation as measured by functional Near Infrared Spectroscopy (fNIRS). fNIRS was used for the detection of brain activation abnormalities in schizophrenia, while patients performed the neuropsychological tests as used in this proposal, but has never been used in at-risk states (as such fNIRS is a time- and cost-effective technique). We hypothesize that the predictive power of both NIRS measurements and neurocognitive tests is better than that of neurocognitive test results alone. We will further explore differences between early onset (age 13-17) and adult onset (age 18-25) at-risk persons with fNIRS techniques additionally applying fNIRS to a sample of 40 adult onset at-risk persons recruited in our early detection and intervention centre (FETZ Bern) as in-house contribution. The NIRS device was sponsored by SNF (R'Equip 326030_139238).(4) We will assess the **outcome of AtRisk** including stability of at-risk criteria, course of psychosocial functioning as well as development of other psychiatric disorders and its potential relation to stressful life events.

(5) We will retrospectively assess the **prevalence of at-risk criteria prior to the onset of psychotic symptoms (in the prodromal phase) in a first admitted EOP** sample. Avoiding the selection bias towards people with at-risk criteria in prospective studies of at-risk persons, this allows an estimation of the *sensitivity* (i.e., rate of subjects with at-risk criteria in those with psychosis). Since at-risk criteria in the prodromal phase will be assessed retrospectively, in line with Schultze-Lutter et al. (2010), BLIPS cannot validly be distinguished from the actual onset of the first psychotic episode, nor can the amount and timing of decline of social functioning in the prodrome be validly assessed. The sensitivity of APS and/or COPER in adult first-episode psychosis was reported at 87% (ibid.). Based on previous reports that certain at-risk criteria appear to be more common in minors (see 2.1.2.), **we expect an equal or higher *sensitivity* in EOP compared to AOP**.

(6) We will assess the **prevalence rates and distributions of at-risk criteria** and additional potential predictors **in a general population sample (GPS) as well as a clinical sample (ClinS),** for which an increased prevalence of subsequent schizophrenia or psychotic symptoms has been reported (*Appendix 2*; Rubino et al. 2009): Attention-Deficit Hyperactivity Disorder (ADHD; all subtypes), anxiety disorders (restricted to Social Phobia and Specific Phobia) and Obsessive Compulsive Disorder (OCD), Eating Disorders (ED; Anorexia Nervosa and Bulimia Nervosa) and Asperger's Disorder. The follow-up of this group allows the estimation of *specificity* (i.e., rate of subjects without at-risk criteria among those without conversion) as well as *negative predictive power* (i.e., rate of subjects without conversion in those without at-risk criteria). Further, the assessment of GPS allows an estimation of whether or not at-risk criteria and symptoms are merely frequent, potentially mainly stress-related, phenomena of no clinical significance in non-help-seeking, non-clinical CAD. Based on preliminary data in GPS (2.1.2), we assume at least a 2%-rate of subjects with any at-risk criterion. In ClinS, a higher, i.e., 2- to 3-fold, prevalence rate (at least 6%) of at-risk criteria is assumed.

(7) Potential gender and age differences in the frequency and distribution of at-risk criteria and potential other predictors will be examined across all three groups. Due to the age distribution of first-episode psychoses, we expect a higher symptom load with increasing age. As regards gender, we expect more pronounced attenuated positive symptoms and neurocognitive deficits in girls and more pronounced negative symptomatology in boys particularly within the help-seeking samples (Addington & Schultze-Lutter 2006, Walder et al. 2008). A potential interaction of age and gender on psychopathology and neurocognition will be preliminary explored.

This study will be the first to examine the validity of current at-risk criteria, which have been developed in adults and mixed-age samples, **for CAD** and provide starting points for their revision.

To this, the results will have the following implications:

1. A completely different or additional set of at-risk criteria for CAD is needed, if the *sensitivity* of 'fulfilling any current at-risk criterion' is low: If at-risk criteria are not reported in EOP for the prodromal phase at an adequate frequency, many EOP will be missed by applying current at-risk criteria only.
2. A revision of at-risk criteria for CAD is needed, if the *positive predictive power* of at-risk criteria is low in AtRisk and if the *specificity* and *negative predictive power* is low in ClinS and GPS; if their *prevalence in GPS* is high, a revision is also required. Further, if APS are frequent in GPS and APS are not accompanied by functional decrease or burden, the **clinical validity of the proposed Attenuated Psychosis Syndrome (DSM-5)** needs to be reconsidered in this age group.

The revisions of at-risk criteria may include the addition of predictors, the elimination of single criteria and/or their redefinition in terms of frequency- and/or time-criteria.

2.3.2. Detailed work plan

2.3.2.1. Sample & Recruitment

Sample, inclusion and exclusion criteria

Subjects will be ascertained in **2 Swiss and 1 German CAD psychiatric centres with established early detection services**. Sample sizes are based on both case loads per centre and a conservative estimation of attrition rates. General *inclusion criteria* are: (i) sufficient language skills in German, French or English and (ii) IQ > 70. A disturbance due to the direct physiological effects of a general medical condition is a general *exclusion criterion*. The following **groups** will be **recruited**:

(group 1) **Help-seeking at-risk CAD** (**AtRisk; n=209; age 8-17.9)** defined by the presence of at least any one BS or UHR criterion (*Appendix 1*). *Additional exclusion criteria* are (i) a life-time diagnosis of a psychotic disorder (affective or non-affective psychoses except for Psychosis NOS when conferring to BLIPS criteria); (ii) at-risk symptoms unequivocally due to the direct physiological effects of a substance (e.g., a drug or medication). Note: Substance abuse or dependency *per se* is no exclusion criterion in this group, because a large proportion of subjects with at-risk criteria use substances, primarily cannabis (Rosen et al. 2006), and their exclusion would limit the study results' generalizability to clinical populations.

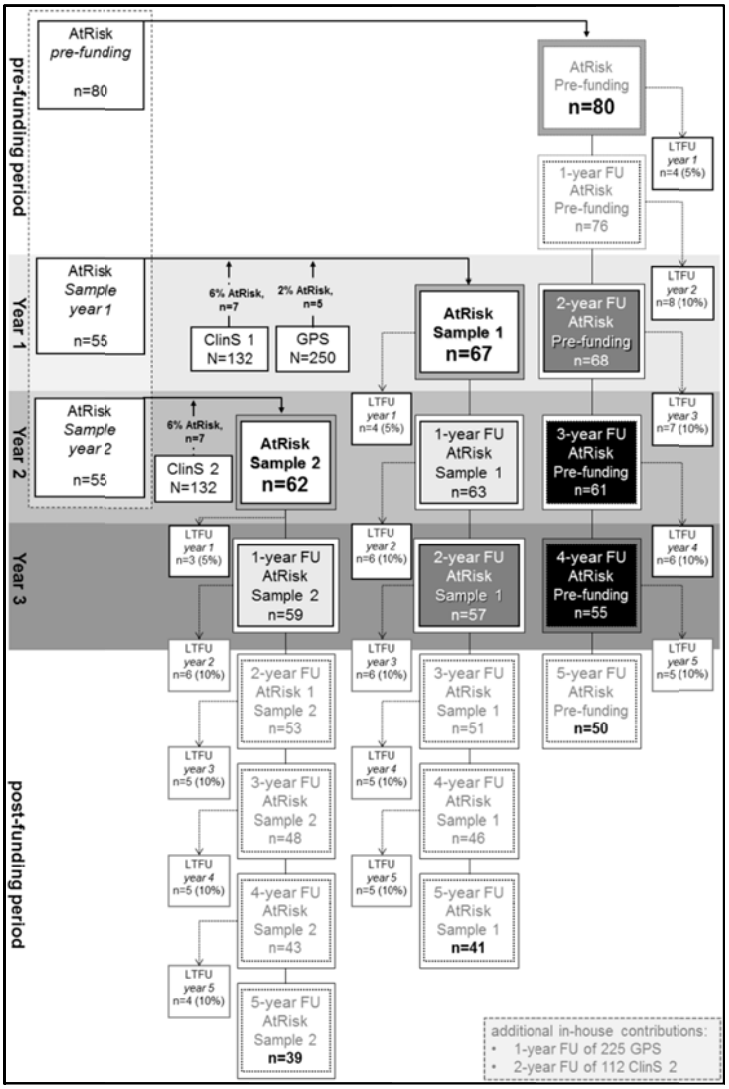
(group 2) **An early-onset psychosis sample** (**EOP, n=100; age 8 onwards with psychosis onset before age 18.0)** first admitted for a Schizophreniform Disorder, Schizoaffective Disorder, Schizophrenia, Brief Psychotic Episode, Delusional Disorder or an affective disorder with psychotic features. *Additional exclusion criteria* are (i) Psychosis NOS for their overlap with BLIPS; (ii) a psychosis unequivocally due to the direct physiological effects of a substance (e.g., a drug or medication).

(group 3) **A non-psychotic clinical sample** (**ClinS; n=264; age 8-17.9)** with a DMS-IV diagnosis, for which an increased prevalence of subsequent schizophrenia has been reported (*Appendix 2*): ADHD, anxiety disorders (Social Phobia and Specific Phobia) and OCD, ED (Anorexia Nervosa and Bulimia Nervosa) and Asperger's Disorder. Comorbidity with any other psychiatric disorders will not serve as an *additional exclusion criterion* except for a life-time diagnosis of any psychotic disorder or Bipolar Disorder I and II. Further, patients with current antipsychotic treatment or at-risk criteria are excluded from ClinS. Note: Patients intended for ClinS fulfilling at-risk criteria will be recruited into AtRisk and replaced in ClinS. To match the expected age and gender distribution of at-risk children, the following *age and gender stratification* across the ClinS as a whole will be pre-specified: age 16-17.9=60%; 14-15.9=25%; 8-13.9=15%; and male:female ratio of 2:1 (Kirkbride et al. 2006). Stratification will be centrally monitored by the leading centre (Bern).

(group 4) **A general population sample** (**GPS; n=250; age 8.0-17.9)** will be recruited with an equal distribution across age groups (50 per 2-year age-group).

Recruitment procedure

Help-seeking AtRisk will be recruited in the three early detection services of Bern, Cologne and Zurich. EOP and ClinS will be recruited from in- and outpatients of all three centres. Both AtRisk and ClinS will be recruited within the first two years, **EOP** within the full three-year period (**10 per centre/year**).



80 AtRisk have already been recruited; these AtRisk have already received their baseline assessment; and 76 of them (4 drop-outs) will have received their 1-year follow-up within the pre-funding period (*Figure 1*). Thus, to collect our final sample of 209 AtRisk, only 55 help-seeking **AtRisk remain to be recruited** in the three participating early detection services in year 1 and 2 (i.e., **18-19 per centre/year**). The expected additional 14 AtRisk from ClinS (6% out of 264) and 5 from GPS (2% out of 250) will complement the AtRisk sample (*Figure 1*). Although the number to recruit per year seems realistic in light of the pre-funding recruitment of AtRisk in the three centres so far, **recruitment of AtRisk continues** during the pre-funding period, thus providing a further **safety margin**.

This **graduated recruitment of AtRisk effects the number of follow-ups carried out within the funding period**: the 80 pre-funding AtRisk already assessed at baseline and year 1, will receive their 2-, 3- and 4-year follow-up; the AtRisk recruited within the first year of funding will receive a 1- and 2-year follow-up; those recruited within the second year of the study a 1-year follow-up (*Figure 1*).

To limit organizational work load, GPS are recruited in Bern only. As in our epidemiological telephone survey (*see 2.2.*), the Agency for Informatics and Organisation of the Canton Bern will draw a random sample of 500 persons (incl. addresses) equally distributed across age and gender. First contact will be established by an information letter, personally addressing each potential participant and his/her parents. Subsequently, parents and their children will be contacted by phone, informed in detail and asked to give consent. For children below age 16, parents will be contacted first. The **recruitment of the 50 16- and 17-year-old GPS** will be **supported by our telephone study**: interviewees of this age will be asked for consent to be informed about an **extended** face-to-face study and recruited this way. The two recruitment procedures were already successful in a **feasibility study** in that **31 GPS** have already been included, and 19 more will be included before the funding period (2.5.1.). GPS will be paid an incentive of CHF 30,- for baseline participation and CHF 20,- for each follow-up. For follow-up assessments of ClinS, an incentive of CHF 20,- (Euro 15,-) after each follow-up will be given.

2.3.2.2. Assessments

At-risk criteria and at-risk symptoms

In AtRisk, ClinS, GPS as well as in EOP, the following interviews assessing at-risk criteria and symptoms will be carried out.

- the Schizophrenia Prediction Instrument, Child & Youth version (**SPI-CY**; Schultze-Lutter & Koch 2010) for the evaluation of the 14 basic symptoms included in COPER and COGDIS (*Appendix 1*)

and other potentially relevant symptoms of the domains 'adynamia', 'perception disturbances', 'neuroticism' and 'thought and motor disturbances'.

- the Structured Interview for Prodromal Syndromes (**SIPS**; McGlashan et al. 2010) incl. a revised version of the 'Global Assessment of Functioning' (**GAF**) **scale** for the evaluation of the five APS and three BLIPS as well as the 'genetic risk and deterioration' criterion of the UHR criteria (*Appendix 1*) and other potentially relevant symptom domains, i.e., negative syndromes, disorganization syndromes and general psychopathological syndromes.

Conversion criteria

As a continuation of the BLIPS definition, a conversion to psychosis is defined by the presence of psychotic symptoms, i.e., hallucinations (SIPS P4 = 6), delusions (SIPS P1, P2 and/or P3 =6) or formal thought disorders (SIPS P5 = 6), for more than one week. The type of psychosis will be assessed with the M.I.N.I. KID six weeks after the onset of psychosis.

Clinical and sociodemographic variables potentially moderating conversion to psychosis

To reveal variables potentially enhancing the evaluation of the risk of psychosis beyond the currently employed risk criteria, the following assessments will be carried out:

- the Mini-International Neuropsychiatric Interview for Children and Adolescents, **M.I.N.I. KID** (Sheehan et al. 1998) for the assessment of past and present mental disorders according to DSM-IV and ICD-10; the M.I.N.I. KID will also be used for the assessment of past and present affective or non-affective psychotic disorders that serve as exclusion criterion in the non-EOP groups and as a validation of clinical diagnosis in the EOP group. The M.I.N.I. had been shown to possess a good construct validity with SCID I, CIDI and expert diagnoses as well as good interrater- and retest-reliability (ibid.).
- a **sociodemographic questionnaire** incl. gender, age, highest level of school graduation/current school as well as years of education, current occupational level, highest level of training of each parent, migration background and family history of psychiatric disorders as well as developmental milestones, obstetric complications and enuresis/encopresis.
- the Social and Occupational Functioning Assessment Scale (**SOFAS**) of DSM-IV (APA 1994) for symptom-independent assessment of psychosocial functioning, highest within last 12 months and current. In addition, the Global Functioning: Social Scale (**GF: Social**; Cornblatt et al. 2007) will be assessed as one of the predictors identified by the NAPLS study (Cannon et al. 2008).
- The Munich Life Event List (**MEL**; Maier-Diewald et al. 1983) will be used for the assessment of 85 positive and negative life events and social conditions in 12 social role areas along with a rating of their subjective burden and positive or negative impact. The MEL possesses good test-retest reliability and can assess life events over several years (Wittchen et al. 1989).

Treatment documentation at follow-up

Treatment, service use and medication for mental problems will be assessed with the two respective sections of the Client Service Receipt Inventory – European Version (CSRI-EU; Chisholm et al. 2000).

Neuropsychological variables potentially moderating conversion to psychosis

For the assessment of the four neuropsychological domains repeatedly reported to enhance prediction of psychosis in at-risk samples, i.e., verbal fluency, verbal and working memory as well as processing speed (*see 2.1.1.*), the following tests - all suitable for children of age 8 and older - will be carried out:

- Verbal executive functions are measured by the Regensburger Wortflüssigkeitstest (**RWT**; Aschenbrenner et al. 2000), i.e., the mean sum of the lexical and semantic category tasks.
- The Verbaler Lern- und Merkfähigkeitstest (**VLMT**; German version of the Auditory Verbal Learning Test; Helmstaedter & Durmen 1990) provides a verbal memory measure for immediate recall after one to five learning trials of word lists. The mean number of correct recalls across all five trials will enter the analyses.
- As a measure of working memory, the paper-pencil version of the Subject Ordered Pointing Task (**SOPT**; Petrides & Milner 1982) is carried out. Across 3 sessions of 12 trials the number of errors, i.e., pointing to an object already chosen on a previous trial, will be calculated.
- The Zahlen-Symbol-Test (**ZST**) of the HAWIK / WIE (German version of the Digit-Symbol Test) and the Trail-Making Test A and B (**TMT**; Reitan 1992) provide measures for the speed of visual information-processing and visuomotor coordination.
- The German version of the Peabody Picture Vocabulary Test (**PPVT**; Dunn & Dunn 1981), a measure of verbal IQ highly correlated with total IQ, is used to control for general effects of IQ.

Assessment of genetic and fNIRS data

- Saliva (at amounts sufficient for genetic and epigenetic analyses) will be collected in AtRisk at baseline and at 1- and 2-year follow-ups and parental saliva samples at any one time point for genetic analyses. Saliva sampling is the least invasive technique allowing for an estimated participation rate of 70% of the total sample. We expect a final sample of 130 at-risk CAD for genetic analyses (70% of 190, all of which can be assessed at any follow-up assessment) and 100 for epigenetic analyses (70% of 144, as saliva collection at baseline cannot be done in retrospect in Bern's and Cologne's pre-funding AtRisk, while saliva of Zurich's pre-funding AtRisk was already collected at baseline. (Epi)genetic analyses will be performed by the laboratory of Prof. Walitza using real-time PCR and HRM methodology. The top 10 gene polymorphisms found in adult schizophrenia (www.szgene.org) will be specified as well as the up-to-date candidate gene polymorphisms implicated in the prediction of conversion to psychosis.
- fNIRS will be applied, while the above mentioned neuropsychological tests are performed. Data will be analysed in cooperation with Prof. Thomas Dierks' group in Bern (see support letter).

Assessment procedure, training and quality assurance

The recruiting early detection services have agreed on all clinical assessments of help-seeking AtRisk being carried out by a well-experienced clinician of their early detection team (*see supporting letters*). Research fellows employed for the study will assist them and carry out neuropsychological and follow-up assessments in AtRisk and all assessments in ClinS, GPS and EOP. To warrant good **quality of assessments**, research fellows will receive intensive training, esp. in the main psychopathological assessments (SPI-CY, SIPS), aiming at a rater concordance rate (incl. already experienced ones) with an expert (FSL) of at least 95% (full agreement on symptom presence, ±1 on symptom severity). Continuous supervision by the local experienced clinician and monthly telephone case conferences with FSL will further ensure quality. Bi-annual interrater-reliability assessments, particularly for SPI-CY and SIPS, will provide additional quality assurance. All pre-funding AtRisk and EOP were assessed by clinicians extensively trained and supervised by FSL. As satisfying interrater reliabilities are reported for the assessment of BS (by SPI-A) and SIPS after only 5 trainings sessions (Schultze-Lutter et al. 2007a; McGlashan et al. 2010), this extensive training will grant excellent interrater reliability.

Baseline assessments: After informed assent and consent is provided, interviews with AtRisk, ClinS and EOP and their parents will be carried out in the hospital; interviews with GPS and their parents will be carried out either at home or in the FETZ Bern. In line with the recommendations of the M.I.N.I. KID, children under 13 are interviewed together with a parent. Questions are directed to the child, but the parent is encouraged to interject if feeling that the child's answers are inaccurate.
In all age groups, a short anamnestic interview with a parent will be carried out. Furthermore, children's information on psychosocial functioning will generally be validated with a parent.

Assessments can be split according to subjects' capacity without loss of quality. To assure economic assessment and avoid redundancies, SIPS, SPI-CY, M.I.N.I. KID, and questions necessary to rate GF: Social and SOFAS are combined into one interview; respective items are rated after conclusion of the interview, taking into account all available information. Such a combined, individually tailored assessment of psychopathology is the standard procedure in the recruiting early detection services, and has been experienced to be positively perceived by interviewees and ensure reliable information.

All instruments will be assessed in AtRisk, ClinS and GPS at baseline (*Table 1*). While in ClinS and GPS, all assessments are carried out within the framework of the study, in help-seeking AtRisk, SPI-CY, SIPS and M.I.N.I. KID (psychosis section) as well as basic sociodemographic data are parts of the pre-study routine diagnostic assessment. Thus, the **average assessment time strictly being part of the study** (incl. 1h neuropsychological assessment and 0,5h life event assessment in all groups) is estimated based on prior experiences at **150 min. in AtRisk, 270 min. in ClinS** and **210 min. in GPS** (slightly lesser time than for ClinS for the expected lesser number of symptoms in GPS).

In EOP, following clinical stabilization (defined by PANSS 'conceptual disorganization' ≤ 3 and appraisal of the psychiatrist in charge), assessments will be restricted to sociodemographics, M.I.N.I. KID, (social) functioning and the selected at-risk criteria (APS, COPER, COGDIS and genetic risk). At-risk symptoms as well as psychotic symptoms (necessary to establish onset of psychosis) are assessed according to SPI-CY and SIPS in retrospect for the time of their occurrence. Retrospective dating will follow the 'anchor-point' method well-established within the Age-Beginning-Course study (Maurer & Häfner 1995) and successfully used in our retrospective study of first-episode psychosis patients (Schultze-Lutter et al. 2010). The **average interview time of EOP** is estimated at **120 min.**

Follow-up assessments: Within the study period, **AtRisk** will be followed annually for conversion to psychosis, other psychiatric disorders (M.I.N.I. KID or M.I.N.I. for adults) as well as for stability of at-risk criteria and meanwhile occurred/continued life events (*Table 1*). Annual conversion assessments include timing of psychosis onset (in months). Furthermore, the participating early detection services

agreed on continuing these follow-up assessments annually over the subsequent 2-4 years allowing a final 5-year follow-up. Treatment will not be pre-specified but documented at follow-ups (CSRI-EU). Face-to-face follow-up contacts with AtRisk and their parents are preferred, but phone interviews are also possible (e.g., if moved away). Good agreement between face-to-face and telephone assessed at-risk criteria was shown in our pilot study (SNF 32003B_135381). Follow-ups are estimated at **140 min.** each. See *Figure 1* for expected sample sizes at follow-up and loss-to-follow-up rates.

Table 1: Flow chart of assessments within funding period

Month	**1 (baseline)**				**12**			**24**		
Group	EOP	AtRisk	ClinS	GPS	AtRisk	ClinS	GPS	AtRisk	ClinS	GPS
At-risk criteria only	■*				■	■	■	■	■	■
SPI-CY, all		■	■	■						
SIPS, all		■	■	■						
M.I.N.I. KID, all	■	■	■	■	■			■		
psychosis section only						■	■		■	■
Sociodemographics	■	■	■	■						
SOFAS, GF: Social	■	■	■	■	■			■		
MEL		■	■	■	■	■	■	■	■	■
Neuropsychology		■	■	■						
Saliva samples		■			■			■		
CSRI-EU					■			■		

* assessed retrospectively.

In **ClinS** and **GPS**, conversion to psychosis and new emergence of at-risk criteria will be assessed at 1- and 2-year follow-ups with patients and parents via phone interviews of approximately **90-min.** mean duration preceded by a reminder letter (*Table 1*). Annual loss-to-follow-up rates for both groups are estimated at 10%. The participating centres agreed to perform the **2-year follow-up of ClinS recruited in the second year** (n=132) after termination of funding as **in-house contribution**.

2.3.2.3. Statistics

Power calculation

Primary aim: Based on our main hypothesis (1-year conversion rate in CAD that is lower than the generally assumed 20% rate in adults), at the expected sample size of **198 AtRisk with a 1-year follow-up**, already an 8%-deviance, i.e., a 12-months conversion rate of 12% as reported by Ziermans et al. (2011), will be detected at an α-level of 5% (ε) and a **power=93%** (1-φ) applying a 1-sided 1-dimensional χ^2-test. In addition, if only the **123 AtRisk with a 2-year follow-up** are taken into account, an increase in annual conversion rates as reported by Cornblatt et al. (2007), i.e., from six to 13%, can be detected with the same, but two-tailed method of analysis at a level of α=.05 with a **power=73%**, and a decrease in conversion rate from 12% to 4% as reported by Ziermans et al. (2011) can be detected at a level of α=.05 with a **power=92%**.

Secondary aims: Assuming no lower sensitivity compared to adults, the expected sample size of **100 EOP subjects** will allow the detection of a 10%-decrease from the assumed 87% of subjects with COPER or APS found in an adult first-episode psychosis sample (Schultze-Lutter et al. 2010) at a 5% error level to falsely accept the H_0 (ε) and a **84%** level to correctly accept the H_0 (1-φ).

The targeted sample size of **250 GPS** will allow the detection of a 5%-increase from the assumed conservative prevalence of at-risk criteria of 2% at α=.01 (.05) and **power=95% (99%)**.

In ClinS, which is expected to have an at least twofold incidence of psychosis, the targeted sample size of **264 ClinS** already allows the detection of an 5%-increase from the assumed lowest rate of at-risk criteria of 6% at α=5% and a **power=90%**.

Data analyses

Primary aim: To test our main hypothesis of a 1-year conversion rate in the CAD AtRisk sample that is lower than the generally assumed 20% rate in adults, a **1-sided 1-dimensional χ^2-test** will be carried out. A **2-sided 1-dimensional χ^2-test** will be used to test a change in conversion rate between year 1 and 2. Using 6-month intervals, i.e., 4 follow-up points, the trend in conversion rates – linear

(increasing over time) or quadratic (first increasing, then decreasing) – will be further tested using the polynominal contrast option of the 1-way independent ANOVA.

Secondary aims: One-sided 1-dimensional χ^2-tests will also be used to test for significant deviances from the expected sensitivity of at-risk criteria in EOP as well as from their expected prevalence in GPS and ClinS. In addition, the two reported regression equations of clinical and sociodemographic predictors, proposed to enhance risk assessment within an at-risk sample (Cannon et al. 2008; Ruhrmann et al. 2011), will be applied to AtRisk data with conversions accounted for at month 18 for the EPOS equation and 24 months for the NAPLS equation. Their performance in our CAD AtRisk will be compared to those reported (ibid.), again by 1-sided 1-dimensional χ^2-tests.

Besides descriptions of prevalence rates and distributions of at-risk criteria and potential clinical, sociodemographic, neuropsychological, genetic and functional imaging predictors in AtRisk, the main predictors of conversion at 12 and 24 months will be identified in line with the methods applied in EPOS (Ruhrmann et al. 2011): To determine the risk of conversion by the cumulative hazard rate measuring the incidence rate exactly at time *t*, Kaplan-Meier **survival analysis** will be employed. AtRisk with survival times exceeding the respective follow-up will be considered censored at the end of month 12 and 24 respectively. Survival curves will be compared by log-rank test. The variables' effect on survival time (i.e., time to conversion) will be estimated with the Cox proportional hazard model with continuous data entering analyses as raw and categorized data. Item scores will be dichotomized according to the cut-off values of the at-risk criteria of the respective scale, i.e., generally at '>2'. Summary scores and continuous data will be dichotomized at their respective cut-off combining high specificity (≥.70) with sufficient sensitivity (≥.25) derived from explorative receiver operating characteristic (ROC) curve analyses.

As it is expected that the number of AtRisk with conversion will be too small to allow the simultaneous analysis of all variables, **predictors will be selected in several steps**: First, covariates will be computed individually and chosen for further analyses, when changes of the -2 log-likelihood of the model and the Wald statistic become significant (p<.10). Next, backward multivariate Cox regression analyses will be performed within the respective domains (i.e., at-risk criteria, each of the four SPI-CY dimensions, each of the four SIPS subscales, global and social functioning, genetic risk, sociodemographic data, comorbidity, substance abuse and neuropsychology) at a liberal level of significance (p<.15). Retained covariates will enter a multivariate backward regression (p<.05) across domains, introducing domains block-wise. For the resulting covariates, interactions will be calculated and kept in the model if significant (p<.05). Finally, the remaining covariates will be analyzed together forward and backward to exclude effects of blocking.

In case of conversion to psychosis occurring within ClinS and GPS in sufficient number (≥10), the same methods to identify predictors of conversion will be applied with the only exception that the domain 'at-risk criteria' cannot be considered.

Using all samples, **diagnostic accuracy measures** of dichotomized variables incl. diagnostic likelihood ratios will be calculated using a 2×2-table. In addition, odds ratios will be calculated by logistic regression analyses and cut-off independent estimations of the diagnostic accuracy of continuous variables will be retrieved from ROC curve analyses.

Further, across the 5 age groups (8-9, 10-11, 12-13, 14-15 and 16-17) an increasing linear trend will be tested using the polynominal contrast option of the 1-way independent ANOVA in AtRisk, ClinS and GPS. Gender differences in psychopathology will be examined by Mann-Whitney-U-tests, those in neurocognition by ANCOVA with the PPVT (estimate of premorbid verbal IQ) as covariate. A potential interaction of age and gender will be explored by 2-way independent ANOVA.

Missing data & Data management

During data collection, item non-response may occur when the participant is unable to answer a particular question or the interviewer fails to ask the question by mistake; both rarely occurs to the experiences made in the early detection services. Occasional missing data, however, will be excluded only from analyses in that they appear.

The leading centre Bern will provide data entry files (SPSS) for all centres to allow easy pooling of data. Data will be anonymized by a centre-case-number code to allow pooling of follow-up data. All research fellows will be trained in data handling and data entering immediately after conclusion of each assessment in order to allow immediate queries in case of missing data. To assure quality, data will be entered twice and compared.

2.4. Timetable & Milestones

Work package 1

Within the **first three months**, research fellows (i.e., postgraduate psychologists) will receive intensive **training** in interview techniques and study instruments in Bern by BGS & FSL and 'on-the-job' by the experienced clinicians in the respective early detection centres, who were previously trained by FSL in the assessment of SIPS and SPI-CY and will participate in interrater reliability tests before supervising the research fellows. By end of month 3, the concordance rate in both research fellows and experienced clinicians with an expert rating (FSL) should at least be 95% (*Figure 2*).

Work package 2 & 3

Recruitment and baseline assessments will continue at day 1 of the funding period in help-seeking AtRisk performed by experienced clinicians who will further train research fellows (training on-the-job). Both Swiss research fellows will be employed in Bern, one will work in Bern, the other in Zurich. One German research fellow will be employed and work in Cologne.

In month 1-12, 46 ClinS (n=44+2 replacements), 10 EOP and 18-19 help-seeking AtRisk will be recruited and baseline assessments carried out in each centre. 200 GPS will be recruited and assessed in Bern by the two Swiss research fellows (50 additional in the pre-funding period). Data entry and quality control will be provided by the research fellow in Cologne. Thus, the work load for GPS will roughly be equal for all research fellows. Furthermore, 1-year follow-ups of the about 25-26 pre-funding AtRisk per centre (i.e., 80 minus 4 drop-outs) will be performed by each research fellow. Based on our clinical and research experience in CAD in general and in the respective early detection centres in particular, the following work load related to work package 2 is assumed for each research fellow (50%) in year 1:

- Recruitment and assessment of 44 ClinS plus 2 replacements of ClinS meeting at-risk criteria (4.5h/patient = 207h + 50h organisational work (orga); **257h**)
- Study assessments of 18-19 AtRisk seeking help in the respective early detection service (2.5h/patient = 46h + 20h orga; **66h**)
- Recruitment and assessment of 10 EOP (2h/patient = 20h + 10h orga; **30h**)
- 2-year follow-up assessments of 23 pre-funding AtRisk (2.3h/patient = 53h + 20h orga; **73h**)
- Data entry and quality control (henceforth data entry) of 100 subjects (at 1.5h/subject; **150h**)
- Ongoing supervision and monitoring, interrater-reliability tests (**80h**)
- Recruitment and assessment of 200 GPS (3.5h/subjects = 700h + 150h orga + 200h data entry; 1'050h). Divided by three, each research fellow will roughly spend **350h**.

In month 13-24, 10 EOP, 18-19 help-seeking AtRisk and 46 ClinS (n=44+2 replacements) will be recruited and baseline assessments carried out in each centre. Furthermore, follow-ups of 39 ClinS and altogether 41 AtRisk per centre, 225 GPS will be carried out. The following work load is assumed for **each research fellow (50%) in year 2**:

- Recruitment and assessment of 44 ClinS 2 plus 2 replacement (4.5h/patient = 407h + 50h orga; **257h**)
- Study assessments of the 18-19 help-seeking AtRisk (2.5h/patient = 46h + 20h orga; **66h**)
- Recruitment and assessment of 10 EOP (2h/patient = 20h + 10h orga; **30h**)
- Data entry of 74 subjects (at 1.5h/subject; **111h**)
- 1-year follow-up of 39 ClinS 1 (1.8h/patient = 70h + 20h orga + 58h data entry; **148h**)
- 1-year follow-up of 21 AtRisk 1 (2.3h/patient = 48h + 20h orga; + 42h data entry; **110h**)
- 3-year follow-up of 20 pre-funding AtRisk (2.3h/patient = 46h + 20h orga + 40h data entry; **106h**)
- Generation of address data file, preparation and timely posting of reminder letters (**75h**)
- Ongoing supervision and monitoring, interrater-reliability tests for year 2 (**80h**)
- Data base merging, analyses of baseline data and report; topics will be split amongst research fellows (**50h**)
- (1-year follow-up of 225 GPS (1.8h/subject = 405h + 60h orga + 338h data entry; 803h). Divided by three, every research fellow would have to spend 268h) These hours exceed the 50% working hours of the research fellows, thus Bern will contribute an additional 50% research fellow as **additional in-house contribution** (803h)).

In month 25-36, EOP (n=10) will be recruited; and follow-ups of altogether 57 AtRisk and 74 ClinS as well as 202 GPS will be carried out; The following work load related to work package 3 is assumed for each research fellow (50%) in year 3:

- Recruitment and assessment of 10 EOP (2h/patient = 20h + 10h orga; **30h**)

- 1-year follow-up of 20 AtRisk 2 (2.3h/patient = 46h + 20h orga + 40h data entry; **106h**)
- 1-year follow-up of 39 ClinS 2 (1.8h/patient = 70h + 20h orga + 58h data entry; **148h**)
- 2-year follow-up of 19 AtRisk 1 (2.3h/patient = 44h + 20h orga + 38h data entry; **102h**)
- 2-year follow-up of 35 ClinS 1 (1.8h/patient = 63h + 20h orga + 53h data entry; **136h**)
- 4-year follow-up of 18 pre-funding AtRisk (2.3h/patient = 42h + 18h orga + 36h data entry; **96h**)
- Preparation and timely posting of reminder letters (**100h**)
- Ongoing supervision and monitoring, interrater-reliability tests for year 3 (**80h**)
- 2-year follow-up of 202 GPS (1.8h/subject = 363h + 60h orga + 303h data entry; 726h). Divided by three, every research fellow will spend **242h**
- (Finalization of data base and first follow-up analyses (**50h**); this will be done by the senior researchers to ensure excellent quality at this important last step of data preparation)

In sum, about 1'012h in year 1, 1'033h in year 2 and 1'040h in year 3 are needed per centre. Thus, a **50% research fellow per centre/year** is required.

The successful conclusion of the interrater-reliability training at month 3 signifies **milestone 1**. The completion of baseline assessments and data entry of ClinS 1, GPS and AtRisk 1 as well as the 2-year follow-up of pre-funding AtRisk is **milestone 2** at month 12. The completion of baseline assessments of AtRisk 2 and ClinS 2, the 1-year follow-ups of AtRisk 1, ClinS 1 and GPS, the 3-year follow-up of pre-funding AtRisk as well as baseline and follow-up data entry and report is **milestone 3** at month 24. Finally, the completion of all EOP assessments, the 1-year follow-ups of AtRisk 2 and ClinS 2, the 2-year follow-ups of AtRisk 1, ClinS 1 and GPS, the 4-year follow-up of pre-funding AtRisk as well as all data entries is **milestone 4** at month 36.

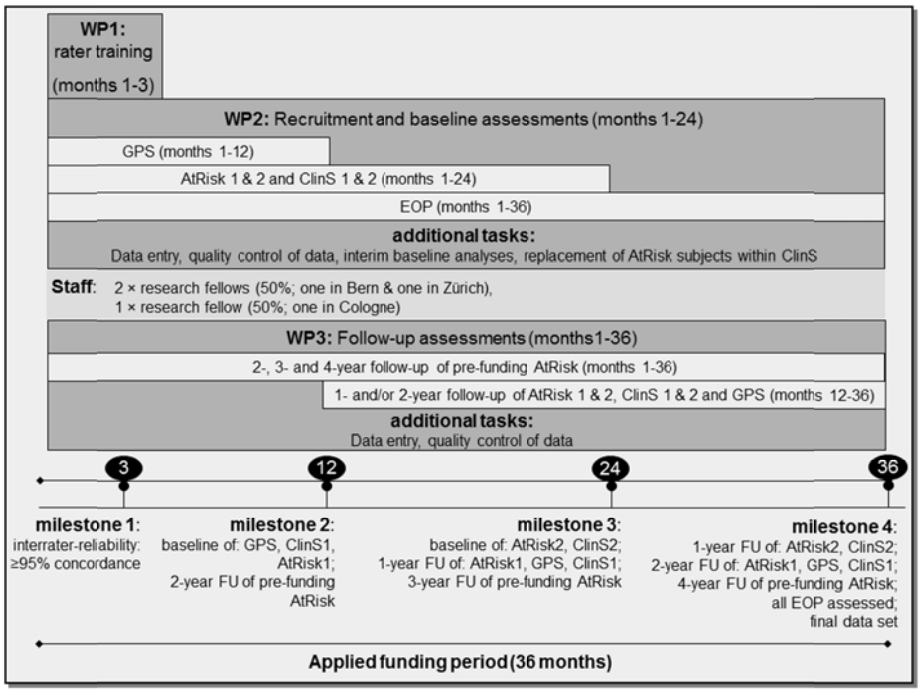


Figure 2: Work packages (WP) and milestones

2.5. Feasibility studies

General population sample: The assumed response rate of 50%, and the planned recruitment and assessment procedure in the GPS sample (2.3.2.1) is tested in a feasibility study. So far 31 subjects have been recruited; of these, 12 were recruited for the additional assessments in a face-to-face setting from 26 eligible 16- and 17-year old participants of the phone survey (response rate: 46%); further 19 8- to 15-year-olds were directly recruited (via KAIO – letter – call) from 40 contacted families (refused: 13 (33%); still indecisive about participation: 6 (15%); excluded: 2(5%)) – thus our 50% response rate seems realistic. Changes, however, had to be made in the average time scheduled for baseline assessments: this was 3.0 hours on average (so far not including the MEL that will have to be assessed retroactively at first follow-up).

At-risk sample: Within the three centres, altogether 80 AtRisk have already been recruited and assessed at baseline during the last 12 to 18 months. Anticipating 4 drop-outs, they will receive their 1-year follow-up within the next 6 months prior to funding. So far, 20 have already received 1-year

follow-up; 10% have converted to psychosis – thus, our design seems feasible and the recruitment rate (18-19 per centre/year) realistic. With these pre-funding AtRisk, however, the MEL will have to be assessed retroactively at the next follow-up.

Need for Swiss-German cooperation

As the incidence especially of AtRisk and EOP is low, a multi-centre approach is necessary to achieve adequate sample size within a 3-year funding period. In order to recruit a sufficient number of AtRisk, it is necessary that an early detection service specifically for CAD is already established. This allows for (i) recruitment starting at day 1 of the study and (ii) the inclusion of already assessed AtRisk subjects (n=25 are already contributed by Cologne and 55 by Zurich and Bern). Furthermore, these three centres were already trained and are continuously supervised by FSL ensuring appropriate quality of assessments. Because clinical early detection services specifically for CAD are still very rare, neither in Switzerland nor in Germany alone, a sufficient number of early detection centres in child and adolescent psychiatric departments exists for a national study. Thus, a bilateral cooperation is inevitable.

2.6. Ethical considerations

Throughout the study, the Declaration of Helsinki and data protection regulations will be closely observed. Further considerations are:

- In order not to violate the 'right not to know' in the non help-seeking GPS, CAD and their parents will not be informed about individual test results. This general policy will already be stated in the information letter. Yet, if need for advice or help is voiced during the interview, information about local mental health / counselling services will be provided. This procedure has been approved by the local ethic committee in Bern and was well accepted in a pilot in adults.
- Based on previous experience, the assessment of at-risk criteria is well perceived by help-seeking patients as well as participants in GPS studies. Assessments can be divided into several sessions according to patient's capacity.
- A general major ethical consideration in early detection research is if and how to convey risk of conversion to psychosis to an individual patient without unnecessary stigmatization. In this study, an individualized, careful approach will be used following the procedure already established in the participating centres: Generally, a symptom rather than a diagnosis (e.g., psychosis) related psychoeducative approach will be followed: For example, instead of speaking of a risk of developing psychosis, it will conveyed that a certain at-risk symptom, e.g., attenuated paranoid ideas, may resolve or become more distressing and less likely to overcome. Psychotherapy and, in individual cases, psychopharmacology will be offered mainly within the established therapeutic networks of each centre.

The protocol has already been approved by the Ethic Committees of the University of Bern and Zurich (*see attachments*), while Cologne has principally approved the protocol pending minor revisions (*document attached*). An amendment for the genetic/epigenetic cooperation (see 2.6.) will be obtained within the review period. All prefunding AtRisk in Zurich and Bern were assessed after the approval of the respective Ethic Committees in the context of this study (Bern) and of ZInEP (Zurich). In Cologne, all prefunding AtRisk gave informed consent for their clinical data to be used for research and for follow-up contacts; after the final approval of Cologne's Ethic Committee, they will sign an informed consent for this study at the first follow-up visit.

2.7. Cooperation with ZInEP regarding genetics and epigenetics

The "Zürcher Impulsporgramm zur nachhaltigen Entwicklung der Psychiatrie" (www.zinep.ch) includes a subproject on both the genetics and epigenetics of the at-risk phenotype in collaboration with the laboratory of Prof. Walitza (director of the University Hospital of Child and Adolescent Psychiatry in Zurich and cooperating partner of this project). ZInEP has collected a large sample of AtRisk adults. Our collaboration will enable us to compare CAD to adults regarding genetic polymorphisms and their epigenetic changes associated with the at-risk phenotype and with conversion to psychosis. Based on ZInEP's recruitment so far, the final sample is estimated at 300-400. The saliva sampling (including the retrospective collection of saliva samples of pre-funding AtRisk) will be contributed by all centres as in-house contribution (estimated at 100 at-risk CAD for epigenetic and 130 for genetic analyses).

2.8. Strengths & Weaknesses of the Study

Our approach has several strengths outlined in the following:

- Multi-centre approach combining expertise in at-risk research (Bern) with substantiated clinical experience in at-risk and general assessments of CAD (Cologne and Zurich)

- Established research cooperation between centres in the field of psychosis (Bern and Zurich in the VESPA study; Bern and Cologne in early detection and genetic studies)
- Established early detection services already using equal baseline assessments of at-risk symptoms and criteria
- Experienced clinicians in early detection services having been trained and supervised by FSL
- Savings of funding costs by substantial centres' in-house contribution:
  - Pre-funding inclusion and assessments of 80 AtRisk (now including 1-year FU) and 50 GPS
  - Identification and major parts of the initial assessments of AtRisk in the early detection centres
  - Additional on-the-job training and ongoing supervision of research fellows, thus also avoiding delayed start of recruitment
  - 1-year FU of GPS and up to 5-year FU of at-risk CAD of GPS
  - Annual follow-ups beyond the funding period (2-year FU in ClinS2 and 2-5 year FU in AtRisk)
  - Assessment of the risk enhancing properties of genetic and functional imaging data
- Availability of comparable data from adult AtRisk samples of the Zurich ZInEP study and of the Cologne FETZ allows direct comparisons of adults and CAD and the pooling of our and ZInEP's genetic as well as epigenetic data for comparative analyses (*see supporting letters*)
- Availability of comparable data on the prevalence of at-risk criteria in adult GPS in Bern (SNF 32003B_135381)

A potential, yet unavoidable weakness of the study lies in the multi-centre approach, as centre effects cannot be excluded despite all efforts of quality assurance thus potentially limiting power.

2.9. Expected Value & Valorisation

In psychosis research, the early detection and intervention has become a main topic within the last two decades. Studies on the generation of at-risk criteria, however, were mainly carried out on adult samples. With interest in this topic expanding, these criteria were later on simply extended to CAD samples without prior investigation into potential special needs of this young age-group. Therefore, our study will be the first to examine the validity of current at-risk criteria as well as of the proposed measures to enhance their accuracy (risk equations, neuropsychology, genetics, imaging data) in CAD and, if necessary, provide starting points for their revision. The **impact of the proposed study on future early detection research strategies** will vary depending on its results: If the sensitivity of 'fulfilling any current at-risk criterion' is low, especially in EOP, a completely **different or additional set of at-risk criteria for CAD** is needed. A more or less **comprehensive revision of at-risk criteria for CAD**, however, is needed, (i) if the positive predictive power of at-risk criteria is low in AtRisk, (ii) if their specificity and negative predictive power are low in ClinS and GPS and/or (iii) if their prevalence in GPS is high, particularly in children. Such revisions may include the addition of predictors, the elimination of single criteria and/or their redefinition in terms of frequency- and/or time-criteria.

The **study's practical and potential economic impact** will be considerable. Early detection of psychoses is meanwhile increasingly applied in clinical and research settings in CAD psychiatry and will be even more so if the proposed Attenuated Psychosis Syndrome will indeed be included in DSM-5 (http://www.dsm5.org/ProposedRevisions/; e.g., Carpenter 2011). The study results will therefore be of high relevance for the future of early detection and intervention strategies in CAD psychiatry in Switzerland and other countries either by providing an empirical basis for applying current at-risk criteria and developing intervention strategies from these or, alternatively, by indicating that especially intervention studies should be put back until appropriate at-risk criteria for CAD have been developed (Schimmelmann et al 2011d). To the latter, the results of our study would lay the groundwork.

Further, the identification of a valid at-risk phenotype in CAD will allow (i) to explore the underlying mechanisms (aetiology) of relevant psychopathological at-risk phenomena in CAD (e.g., associated brain regions and functions as well as genes and biomarkers) and thus facilitate knowledge about the development of psychosis in adolescence - an age group, in which the relevant developmental changes of the brain towards psychosis are assumed to take place (Cannon et al. 2003), and (ii) to further enhance the predictive accuracy of at-risk criteria of conversion to psychosis by neurobiological markers. As regards aetiology, the repeated non-invasive collection of saliva samples allows the retrospective examination of genetic and epigenetic hypotheses comparatively (CAD versus adults) and, potentially, in the subgroup of CAD.

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Appendix 1: At-risk criteria of first-episode psychosis

Ultra-high risk (UHR) criteria according to the SIPS

A. 'Brief Limited Intermittent Psychotic Symptom' Prodromal Syndrome (BLIPS)

- ➲ At least any 1 of the following SIPS P-items scored 6 'severe and psychotic'
  - P1 Unusual Thought Content / Delusional Ideas
  - P2 Suspiciousness / Persecutory Ideas
  - P3 Grandiose Ideas
  - P4 Perceptual Abnormalities / Hallucinations
  - P5 Disorganized Communication
- ➲ First appearance in the past three months;
- ➲ Present for at least several minutes per day at a frequency of at least once per month but less than 7 days

B. 'Attenuated Positive Symptom' (APS) Prodromal Syndrome

- ➲ At least any 1 of the following SIPS P-items scored 3 'moderate' to 5 'severe but not psychotic'
  - P1 Unusual Thought Content / Delusional Ideas
  - P2 Suspiciousness / Persecutory Ideas
  - P3 Grandiose Ideas
  - P4 Perceptual Abnormalities / Hallucinations
  - P5 Disorganized Communication
- ➲ First appearance within the past year or current rating one or more scale points higher compared to 12 months ago;
- ➲ Symptoms have occurred at an average frequency of at least once per week in the past month

C. 'Genetic Risk and Deterioration' Prodromal Syndrome

(1) patient meets criteria for Schizotypal Personality Disorder according to SIPS
(2) patient has 1st degree relative with a psychotic disorder
(3) patient has experienced at least 30% drop in GAF score over the last month compared to 12 months ago

- ➲ [1 and 3] or [2 and 3] or all are met.

Basic symptom criteria

Risk criterion 'Cognitive-Perceptive Basic Symptoms' (COPER)

- ➲ At least any 1 of the following basic symptoms with a SPI-A score of ≥3 within the last 3 months:
  - thought interference
  - thought perseveration
  - thought pressure
  - thought blockages
  - disturbance of receptive speech
  - decreased ability to discriminate between ideas and perception, fantasy and true memories
  - unstable ideas of reference
  - derealisation
  - visual perception disturbances (excl. hypersensitivity to light or blurred vision)
  - acoustic perception disturbances (excl. hypersensitivity to sounds)
- ➲ First occurrence ≥12 months ago

High-risk criterion 'Cognitive Disturbances' (COGDIS)

- ➲ At least any 2 of the following basic symptoms with a SPI-A score of ≥3 within the last 3 months:
  - inability to divide attention
  - thought interference
  - thought pressure
  - thought blockages
  - disturbance of receptive speech
  - disturbance of expressive speech
  - unstable ideas of reference
  - disturbances of abstract thinking
  - captivation of attention by details of the visual field

Appendix 2: Axis I antecedents before 18 years by type of mental disorder (Rubino et al. 2009) and corresponding estimates of the risk for developing schizophrenia within a population with the respective axis I disorder (% disorder in SZ / % disorder in GPS).

Antecedent axis I diagnoses	**General population** (GPS; n=300)	**Schizophrenia** (SZ; n=197)	**Estimated risk of schizophrenia in diagnosis**
	n (%)	n (%)	
Major depressive episode	26 (8.7)	29 (14.7)	1.7
Panic disorder	9 (3.0)	9 (4.6)	1.5
Separation anxiety disorder	58 (19.3)	75 (37.9)	2.0
Social phobia	35 (11.7)	57 (28.8)	2.5
Specific phobia	65 (21.7)	114 (57.9)	2.7
Generalized anxiety disorder	56 (18.7)	60 (30.3)	1.6
Obsessive-compulsive disorder	10 (3.3)	16 (8.1)	2.5
Posttraumatic stress disorder	16 (5.3)	24 (12.2)	2.3
Eating disorders	5 (1.7)	10 (5.1)	3.0
Oppositional defiant disorder	31 (10.3)	41 (20.8)	2.0
Conduct disorder	28 (9.3)	34 (17.3)	1.9
ADHD	29 (9.7)	84 (42.6)	4.4
Inattentive subtype	20 (6.7)	73 (37.1)	5.5
Hyperactive subtype	15 (5.0)	54 (27.4)	5.5
Impulsive subtype	9 (3.0)	43 (21.8)	7.3
Primary nocturnal enuresis	27 (9.0)	56 (28.4)	3.2

Note: The rationale to choose diagnoses for ClinS was a risk of developing schizophrenia of larger 2.5. Enuresis will only be assessed in retrospect and not build an individual subgroup in accordance with the age range of the sample, where enuresis will rarely still be present.

Daten zum Antrag und Verpflichtungen – Projektanträge

Prof. Dr. med. Gerd Lehmkuhl, Köln
Prof. Dr. med. Benno Schimmelmann, Bern
Dr. phil. Frauke Schultze-Lutter, Bern

I. Daten zum Antrag

1 Antragstyp

Lead Agency Verfahren – SNF (lead) & DFG

Programm

Sachbeihilfe ☒

Emmy Noether-Programm ☐

Forschergruppe FOR [Nummer]
Einzelantrag ☐ Koordinationsantrag ☐

Schwerpunkt SPP [Nummer]
Einzelantrag ☐ Koordinationsantrag ☐

Antragsform

Neuantrag ☒
Fortsetzungsantrag ☐

2 Angaben zum Antrag

2.1 Dauer/Titel

Deutscher Titel:

Früherkennung von Psychosen im Kindes- und Jugendalter: Evaluation der Risikokriterien

Englischer Titel:

Early detection of psychosis in children and adolescents: An evaluation of current at-risk criteria

Dauer: 36 Monate

2.2 Fachklassifizierung

Fach:

Medizin

(Biologie, Psychologie)

2.3 Schlagworte

Deutsche Schlagworte:

Früherkennung von Psychosen, Kinder und Jugendliche, Validierung Risikokriterien

Englische Schlagworte:

Early detection of psychosis, child and adolescent, validation of at-risk criteria

2.4 Länder

Schweiz

2.5 Zusammenfassung

Englische Zusammenfassung:

Background: Psychoses have an incidence of about 3% with a peak of first onset around the age of 20; 10 to 15% have an onset before the age of 18. These 'early-onset psychoses' (EOP) are generally considered to have an even poorer prognosis than 'adult-onset psychoses' (AOP) that have repeatedly been shown to cause enormous disability and costs. Currently, an early detection of and intervention in persons with first signs of emerging psychosis is regarded a promising strategy to reduce the burden of this disease. To this aim, two complementary sets of at-risk criteria have been developed on mainly adult samples: (1) 'ultra high risk' criteria (UHR) including attenuated and brief limited intermittent psychotic symptoms and a combination of a genetic risk factor and a recent significant functional decline and (2) the basic symptom criteria (BS) 'cognitive-perceptive basic symptoms' and 'cognitive disturbances'. To date, prevention research in psychosis has mainly been carried out in adult or mixed-age help-seeking at-risk samples, i.e., including a small fraction of mainly older adolescents. And despite some indications that at-risk criteria perform differently in adolescent samples – not least due to developmental aspects, no study has hitherto systematically examined the clinical validity and predictive value of at-risk criteria or of the currently discussed additional neuropsychological predictors of psychosis in child and adolescent (CAD) samples.

Working hypothesis and specific aims: The primary aim is to examine the conversion rate to frank psychosis in an at-risk CAD sample (AtRisk) and thereby the positive predictive power of at-risk criteria. Based on the literature, we expect a lower first-year conversion rate compared to adults (<20%), while the second-year conversion rate (no change, increase or decrease compared the first-year) is unclear. The six secondary aims are: (1) to assess the prevalence rates of at-risk criteria, and sociodemographic and neuropsychological predictors, proposed to enhance predictive accuracy, and to identify the main predictors of conversion to psychosis in AtRisk. We expect a different set of predictors compared to adults; (2) to explore the risk enhancing properties of genetic polymorphisms; (3) to examine the risk enhancing properties of functional imaging data (in a subsample); (4) to assess the general outcome of AtRisk beyond conversion to psychosis and the role of life events in this; (5) to assess the prevalence of at-risk criteria prior to the onset of psychotic symptoms (in the prodromal phase) in a first admitted EOP sample and thereby the sensitivity of at-risk criteria in CAD. We expect an equal or higher sensitivity in EOP compared to AOP; (6) to assess prevalence rates and distributions of at-risk criteria and additional potential predictors of

conversion to psychosis in a general population (GPS) as well as a clinical non-psychotic sample (ClinS) with diagnoses, for which an increased prevalence of subsequent psychosis were reported, allowing for calculation of negative predictive power and specificity estimates; and (7) to explore gender differences in the frequency and distribution of at-risk criteria.

Methods: This is a prospective multi-centre naturalistic 3-year follow-up study (Bern, Zurich, Cologne) on altogether 209 AtRisk, 264 ClinS, 250 GPS and 100 EOP. At-risk symptoms and criteria will be assessed with the 'Structured Interview for Prodromal Syndromes' and the 'Schizophrenia Prediction Instrument, Child & Youth version'. Further, sociodemographics and functioning measures, DSM-IV diagnoses as well as potential neuropsychological predictors of conversion (verbal fluency, verbal and working memory as well as processing speed) will be assessed. AtRisk and ClinS will be recruited over 2 years and followed annually at year 1 and 2, GPS will be recruited in year 1 and followed annually at year 1 and 2. Beyond the funded study period, all participating centres have agreed to further follow-up AtRisk until 5-year follow-up as in-house contributions. Repeated collection of saliva samples will allow genetic/epigenetic analyses.

Expected value: Our study will be the first to examine the validity of current at-risk criteria as well as of proposed measures to enhance their accuracy (e.g., neuropsychology, genetics) in CAD and to provide starting points for their potential revision. With more and more CAD psychiatrists taking an interest in early detection and intervention in psychosis, the results of the proposed project will be received with immense interest by the international research community. The impact of the proposed study on future early detection research will vary depending on its results: If the sensitivity of 'fulfilling any current at-risk criterion' is low, especially in EOP, a completely different or additional set of at-risk criteria for CAD is needed. A more or less comprehensive revision of at-risk criteria for CAD, however, is needed, (i) if the positive predictive power of at-risk criteria is low in AtRisk, (ii) if their specificity and negative predictive power are low in ClinS and GPS and/or (iii) if their prevalence in GPS is high. Such revisions may include the addition of predictors, the elimination of single criteria and/or their redefinition in terms of frequency- and/or time-criteria. Overall, the study's practical and potential economic impact will be considerable especially in light of the current discussion about the role of at-risk criteria in DSM-5 and the potential for further neurobiological research on this phenotype.

Deutsche Zusammenfassung:

Psychosen haben eine Inzidenz von etwa 3% mit einem Ersterkrankungsgipfel zwischen dem 20. und 25. Lebensjahr; 10-15% beginnen vor dem 18. Lebensjahr. Die Prognose von diesen so genannten ‚early-onset Psychosen' (EOP) wird als noch schlechter erachtet als bei den später beginnenden Psychosen (‚adult-onset Psychosen', AOP). Bei den AOPs konnte wiederholt gezeigt werden, dass sie enorme Belastungen und Kosten verursachen. Derzeit wird die Früherkennung von und die Intervention bei Personen mit ersten Anzeichen einer auftretenden Psychose als die vielversprechendste Strategie zur Reduktion der Belastung dieser Krankheit erachtet. Bislang lag der Fokus in der Früherkennungsforschung von Psychosen vor allem auf Stichproben, die aus hilfesuchenden, erwachsenen oder altersgemischten Risikopatienten bestanden. Trotz Hinweisen darauf, dass Risikokriterien aufgrund von Entwicklungsprozessen in jugendlichen Stichproben anders auftreten, wurde bislang weder die klinische Validität noch der prädiktive Wert von Risikokriterien oder die zurzeit diskutierten neuropsychologischen Prädiktoren von Psychosen in Studien mit Kindern und Jugendlichen untersucht.

Das Hauptziel dieser prospektiven Multizenter-Studie (Bern, Zürich, Köln) ist daher die Untersuchung der Übergangsrate in einer Risikostichprobe von Kindern und Jugendlichen und somit die *positive prädiktive Stärke* von Risikokriterien bei Kindern und Jugendlichen zu erforschen. Basierend auf der Literatur wird eine zu Beginn niedrigere (< 20%), aber potentiell steigende jährliche Übergangsrate bei Kindern und Jugendlichen im Vergleich zu Erwachsenen erwartet. Die sieben sekundären Ziele sind:

(1) Erfassung der Prävalenz- und Verteilungsraten der Risikokriterien, bei Kindern und Jugendlichen mit erhöhtem Psychoserisiko (AtRisk), sowie die Erhebung von potentiellen soziodemographischen und neuropsychologischen Prädiktoren. Zudem sollen die Hauptprädiktoren für einen Übergang in eine Psychose identifiziert werden. Wir erwarten bei Kindern und Jugendlichen eine andere Reihe von Prädiktoren als bei Erwachsenen.
(2) Untersuchung genetischer Polymorphismen auf ihre prädiktive Stärke für einen Übergangs in eine Psychose
(3) Untersuchung funktioneller Bildgebungsdaten auf ihre prädiktive Stärke für einen Übergangs in eine Psychose
(4) Erfassung der Stabilität der Risikokriterien, Verlauf des psychosozialen Funktionsniveaus und Entwicklung anderer psychiatrischer Erkrankungen bei der AtRisk-Gruppe.
(5) Erfassung der Prävalenz von Risikokriterien vor dem Beginn von psychotischen Symptomen (in der prodromalen Phase) in einer erstmals behandelten EOP-Gruppe und somit die Untersuchung der Sensitivität der Risikokriterien bei Kindern und Jugendlichen. Wir erwarten in der EOP-Gruppe die gleiche oder eine gar höhere *Sensitivität* als in der AOP-Gruppe
(6) Erfassung der Prävalenz- und Verteilungsraten von Risikokriterien und zusätzlichen potentiellen Prädiktoren von Übergangsraten in eine Psychose in der Allgemeinbevölkerung (‚general population sample') sowie in einer klinischen nicht-psychotischen Stichprobe mit Diagnosen, für welche eine erhöhte Prävalenz für eine nachfolgende Psychose gefunden wurde. Dies erlaubt die Berechnung der *negativen prädiktiven Stärke* und die Schätzung der *Genauigkeit* von Risikokriterien.
(7) Erfassung von Geschlechtsunterschieden in der Prävalenz und Verteilung von Risikokriterien.

Es handelt sich um eine prospektive Multi-Center 3-Jahresstudie (Bern, Zürich, Köln) an insgesamt 209 Risikokindern (AtRisk, 8-18 Jahre alt), 264 klinischen Kontrollen, 250 Kindern und Jugendlichen aus der Allgemeinbevölkerung und 100 EOP. Risikosymptome und –kriterien werden mittels des 'Structured Interview for Prodromal Syndromes' und des 'Schizophrenia Prediction Instrument, Child & Youth version' erfasst. Zusätzlich werden soziodemographische Daten und das psychosoziale Funktionsniveau erhoben, andere DSM-IV Diagnosen sowie potentielle neuropsychologische Prädiktoren eines Übergangs in eine Psychose (verbale Wortflüssigkeit, verbales- und Arbeitsgedächtnis sowie Verarbeitungsgeschwindigkeit). Über die funding period hinaus haben alle beteiligten Zentren eingewilligt, Nachuntersuchungen der Risikokinder bis zum 5-Jahres Follow-up aus Hausmitteln durchzuführen.

3 Beteiligte Personen

3.1 Antragstellende Personen

Bitte machen Sie pro antragstellender Person folgende Angaben:

Akademischer Grad/Titel:	Univ. Prof. Dr. med
Vorname:	Gerd
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Geschlecht:	m ☒ w ☐
Geburtsdatum:	06.09.1948
Deutschsprachig:	j ☒ n ☐
E-Mail-Adresse:	gerd.lehmkuhl@uk-koeln.de
Telefon:	0049 221 478-4370/-4650

Anschrift der Institution, an der das geplante Projekt durchgeführt werden soll:

Uniklinik Köln, Klinik und Poliklinik für Psychiatrie und Psychotherapie des Kindes- und Jugendalters, Robert-Koch-Strasse 10 (Gebäude 53), 50931 Köln

3.2 Andere antragsbeteiligte Personen

Akademischer Grad/Titel:	Prof. Dr. med.
Vorname:	Benno
Nachname:	Schimmelmann
Staatsangehörigkeit:	Deutsch
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Universitäre Psychiatrische Dienste Bern
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4 Beteiligte Institutionen

Sofern weitere Institutionen als Kooperations- oder Industriepartner an Ihrem Vorhaben beteiligt sind, führen sie diese bitte hier mit vollständiger Anschrift auf.

Kooperation mit Prof. Dr. med. Dipl. Psych. Susanne Walitza
Zentrum für Kinder- und Jugendpsychiatrie, Poliklinik
Universität Zürich
Neumünsterallee 3
CH-8032 Zürich

5 Erläuterungen zu den vorgesehenen Untersuchungen

Teil des Antrags sind epigenetische und genetische Untersuchungen. Speichelproben werden auch in Köln gesammelt. Die Verwahrung der Speichelproben und deren genetische Analysen werden in Zürich (Labor Prof. S. Walitza) durchgeführt. Dafür wird es ein Kooperationsvertrag geben.
Ein entsprechendes Amendement zum vorliegenden Ethikantrag wird an den beteiligten Zentren eingereicht. Das entsprechende Votum der Kölner Ethikkommission werden wir der DFG nachreichen.

6 Notwendigkeit der Deutsch-Schweizerischen Kooperation

Da die Inzidenzraten von Kindern und Jugendlichen mit einem erhöhten Psychose-Risiko oder mit Erstpsychosen tief sind, ist ein multizentrischer Ansatz notwendig, damit die angestrebten Fallzahlen innerhalb der 3 jährigen Finanzierungszeit erreicht werden können. Damit speziell eine genügend hohe Anzahl von Risikopatienten rekrutiert werden kann, ist es notwendig, dass ein entsprechendes Früherkennungszentrum bereits etabliert ist, damit (1) die Rekrutierung der Patienten ab dem ersten Tag der Studie (Beginn der Finanzierung) starten kann und (2) ermöglicht es den Einschluss von bereits untersuchten Risikopatienten (n=25 wurden bereits von Köln beigesteuert, 55 von Bern und Zürich). Die drei beteiligten Zentren wurden ausserdem bereits von Frau Dr. phil Schultze-Lutter trainiert und werden von ihr kontinuierlich supervidiert, so dass eine hohe Qualität der Erhebungen gewährleistet ist. Weder in der Schweiz noch in Deutschland allein gibt es eine genügend grosse Anzahl von Früherkennungszentren für Kinder und Jugendliche, die für eine nationale Studiendurchführung ausreichen würden. Dementsprechend ist eine Kooperation beider Länder notwendig.

7 Beantragtes Budget

Zahlen in Euro (für Deutschland) und Franken (Schweizerischer Teil)

Mittel beantragt bei der DFG (in Euro)

Personal:	84'150 (50% E13 über 3 Jahre)
Reisekosten:	3'760 (Forschungsgruppentreffen für Training, Monitoring und Kongressteilnahme Prof. Lehmkuhl)
Verbrauchsmaterial:	364 (Neuropsychologische Tests, Anteil DFG)
Sonstige Kosten:	2'265 (Vergütung von Versuchspersonen)
Total:	Euro 90'539

Gesamtumfang Mittel beantragt bei SNF (in CHF):

Personal:	265'424 (für 2 Zentren jeweils 50% potsgrad. über 3 Jahre)
Reisekosten:	4'750 (Forschungsgruppentreffen und 2 Kongressteilnahmen)
Verbrauchsmaterial:	437 (Neuropsychologische Tests)
Sonstige Kosten:	20'580 (Verbrauchsmaterial)
Total:	CHF 291'191

II. Verpflichtungen

Mit der Einreichung eines Antrags bei der Deutschen Forschungsgemeinschaft (DFG) verpflichten sich alle Antragstellerinnen und Antragsteller,

- die **Regeln guter wissenschaftlicher Praxis** einzuhalten
- die bewilligten Mittel ausschließlich im Interesse einer zielstrebigen Verwirklichung des geförderten Vorhabens einzusetzen, bei der Verwendung und Abrechnung die einschlägigen Richtlinien der DFG zu beachten und insbesondere keine Grundausstattung zu finanzieren.
- der DFG zu den im Bewilligungsschreiben angegebenen Terminen über den Fortgang der Arbeiten zu berichten und Nachweise über die Verwendung der bewilligten Mittel vorzulegen.
- die **Regeln zu den Publikationsverzeichnissen und zum Literaturverzeichnis** bei der Antragstellung beachtet zu haben.
- und - sofern zutreffend -
    - die DFG unverzüglich zu benachrichtigen, wenn ein Antrag auf Finanzierung dieses Vorhabens bei einer anderen Stelle eingereicht wird. Bereits an anderer Stelle eingereichte Anträge bzw. Anträge mit Großgeräten sind in der „Beschreibung des Vorhabens" unter dem Punkt „Ergänzende Erklärungen" aufzuführen.
    - die Vertrauensdozentin bzw. den Vertrauensdozenten ihrer Hochschule von der Antragstellung zu unterrichten.
    - die Generalverwaltung der Max-Planck-Gesellschaft von der Antragstellung zu unterrichten.
    - bei der Planung und Durchführung von **Versuchen am Menschen**, an identifizierbarem menschlichen Material und an identifizierbaren Daten die vom Weltärztebund (WMA - World Medical Association) im Juni 1964 verabschiedete Deklaration von Helsinki (Originaltitel: DECLARATION OF HELSINKI - Ethical Principles for Medical Research Involving Human Subjects) in der jeweils gültigen Fassung und zudem die Bestimmungen des Embryonenschutzgesetzes und des Stammzellgesetzes (StZG), des Arzneimittelgesetzes (§§ 40 - 42 AMG) und des Medizinproduktgesetzes (§§ 17 - 19 MPG) in den jeweils geltenden Fassungen zu beachten.
    - bei **Tierversuchen** die Vorschriften des Tierschutzgesetzes einzuhalten und im Falle der Genehmigungspflicht die Arbeiten erst dann zu beginnen, wenn eine entsprechende Genehmigung vorliegt.
    - bei **gentechnologischen Experimenten** die Vorschriften des Gesetzes zur Regelung von Fragen der Gentechnik vom 20. Juni 1990 (BGBl. 1990 I, S. 1080) zu beachten und die Arbeiten erst dann zu beginnen, wenn die nach diesem Gesetz und den dazu erlassenen Verordnungen erforderlichen Genehmigungen vorliegen.
    - bei Arbeiten mit humanen Embryonalen Stammzellen die notwendige Genehmigung einzuholen und die Arbeiten erst dann zu beginnen, wenn diese vorliegt. Im Bewilligungsfall bleiben die Mittel für diese Arbeiten bis zur Vorlage der Genehmigung gesperrt.
    - wenn Teile des Forschungsvorhabens unter das Übereinkommen über die biologische Vielfalt fallen, das Projekt entsprechend den im "Leitfaden für die Antragstellung von Forschungsvorhaben, die unter das Übereinkommen über die biologische Vielfalt (Convention on Biological Diversity – CBD) fallen" dargestellten Grundsätzen durchzuführen.

☒ Ich/Wir akzeptiere/n alle obenstehenden Erklärungen.

Ich bin/Wir sind damit einverstanden, dass

- die zur Bearbeitung meines Antrags erforderlichen Daten von der DFG elektronisch gespeichert und verarbeitet sowie im Rahmen des DFG-Begutachtungs- und Entscheidungsverfahrens an Gutachter und DFG-Gremien weitergeleitet werden.
- im Falle einer Bewilligung Adress- und Kommunikationsdaten zur Person (Telefon, Fax, E-Mail, WWW-Homepage) sowie inhaltserschließende Angaben zum Projekt (z. B. Thema, Zusammen-fassung, Schlagwörter, Auslandsbezug) in der Projektdatenbank Gepris (www.dfg.de/gepris) sowie - in Auszügen (Name, Institution und Ort der Antragstellerinnen und Antragsteller) - im Teil „Programme und Projekte" des elektronischen Jahresberichts (www.dfg.de/jahresbericht) veröffentlicht werden. Mir ist bekannt, dass ich der Veröffentlichung in elektronischer Form nach Erhalt des Bewilligungsschreibens innerhalb einer Frist von vier Wochen bei dem zuständigen Fachbereich widersprechen kann.

☒ Ich/Wir akzeptiere/n die obenstehenden Erklärungen.

Ort: Köln, Bern
Datum: 30.3.12

Unterschrift (aller antragstellenden Personen)

Deutschland (Prof. Lehmkuhl) Schweiz: (Prof. Schimmelmann, Dr. Schultze-Lutter)

Project description on DFG-homepage

Detailseite

Zurück zur Ergebnisliste

Projekt

Früherkennung von Psychosen im Kindes- und Jugendalter: Evaluation der Risikokriterien

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Fachliche Zuordnung Klinische Psychiatrie, Psychotherapie und Kinder- und Jugendpsychiatrie

Förderung Förderung von 2013 bis 2018

Projektkennung Deutsche Forschungsgemeinschaft (DFG) - Projektnummer 231563730

Projektbeschreibung

Psychosen haben eine Inzidenz von etwa 3% mit einem Ersterkrankungsgipfel zwischen dem 20. und 25. Lebensjahr; 10-15% beginnen vor dem 18. Lebensjahr. Die Prognose von diesen so genannten ‚early-onset Psychosen' (EOP) wird als noch schlechter erachtet als bei den später beginnenden Psychosen (‚adult-onset Psychosen', AOP). Bei den AOPs konnte wiederholt gezeigt werden, dass sie enorme Belastungen und Kosten verursachen. Derzeit wird die Früherkennung von und die Intervention bei Personen mit ersten Anzeichen einer auftretenden Psychose als die vielversprechendste Strategie zur Reduktion der Belastung dieser Krankheit erachtet. Bislang lag der Fokus in der Früherkennungsforschung von Psychosen vor allem auf Stichproben, die aus hilfesuchenden, erwachsenen oder altersgemischten Risikopatienten bestanden. Trotz Hinweisen darauf, dass Risikokriterien aufgrund von Entwicklungsprozessen in jugendlichen Stichproben anders auftreten, wurde bislang weder die klinische Validität noch der prädiktive Wert von Risikokriterien oder die zurzeit diskutierten neuropsychologischen Prädiktaren von Psychosen in Studien mit Kindern und Jugendlichen untersucht.Das Hauptziel dieser prospektiven Multizenter-Studie (Bern, Zürich, Köln) ist daher die Untersuchung der Übergangsrate in einer Risikostichprobe von Kindern und Jugendlichen und somit die positive prädiktive Stärke von Risikokriterien bei Kindern und Jugendlichen zu erforschen. Basierend auf der Literatur wird eine zu Beginn niedrigere (< 20%), aber potentiell steigende jährliche Übergangsrate bei Kindern und Jugendlichen im Vergleich zu Erwachsenen erwartet. Die sieben sekundären Ziele sind:(1) Erfassung der Prävalenz- und Verteilungsraten der Risikokriterien, bei Kindern und Jugendlichen mit erhöhtem Psychoserisiko (AtRisk), sowie die Erhebung von potentiellen soziodemographischen und neuropsychologischen Prädiktoren. Zudem sollen die Hauptprädiktoren für einen Übergang in eine Psychose identifiziert werden. Wir erwarten bei Kindern und Jugendlichen eine andere Reihe von Prädiktaren als bei Erwachsenen.(2) Untersuchung genetischer Polymorphismen auf ihre prädiktive Stärke für einen Übergangs in eine Psychose(3) Untersuchung funktioneller Bildgebungsdaten auf ihre prädiktive Stärke für einen Übergangs in eine Psychose(4) Erfassung der Stabilität der Risikokriterien, Verlauf des psychosozialen Funktionsniveaus und Entwicklung anderer psychiatrischer Erkrankungen bei der AtRisk-Gruppe.(5) Erfassung der Prävalenz von Risikokriterien vor dem Beginn von psychotischen Symptomen (in der prodromalen Phase) in einer erstmals behandelten EOP-Gruppe und somit die Untersuchung der Sensitivität der Risikokriterien bei Kindern und Jugendlichen. Wir erwarten in der EOP-Gruppe die gleiche oder eine gar höhere Sensitivität als in der AOP-Gruppe(6) Erfassung der Prävalenz- und Verteilungsraten von Risikokriterien und zusätzlichen potentiellen Prädiktaren von Übergangsraten in eine Psychose in der Allgemeinbevölkerung (‚general population sample') sowie in einer klinischen nicht-psychotischen Stichprobe mit Diagnosen, für welche eine erhöhte Prävalenz für eine nachfolgende Psychose gefunden wurde. Dies erlaubt die Berechnung der negativen prädiktiven Stärke und die Schätzung der Genauigkeit von Risikokriterien.(7) Erfassung von Geschlechtsunterschieden in der Prävalenz und Verteilung von Risikokriterien. Es handelt sich um eine prospektive Multi-Center 3-Jahresstudie (Bern, Zürich, Köln) an insgesamt 209 Risikokindern (AtRisk, 8-18 Jahre alt), 264 klinischen Kontrollen, 250 Kindern und Jugendlichen aus der Allgemeinbevölkerung und 100 EOP. Risikosymptome und-kriterienwerden mittels des 'Structured Interview for Prodromal Syndromes' und des 'Schizophrenia Prediction Instrument, Child & Youth version' erfasst. Zusätzlich werden soziodemographische Daten und das psychosoziale Funktionsniveau erhoben, andere DSM-IV Diagnosen sowie potentielle neuropsychologische Prädiktaren eines Übergangs in eine Psychose (verbale Wortflüssigkeit, verbales- und Arbeitsgedächtnis sowie

Verarbeitungsgeschwindigkeit). Über die funding period hinaus haben alle beteiligten Zentren eingewilligt, Nachuntersuchungen der Risikokinder bis zum 5-Jahres Follow-up aus Hausmitteln durchzuführen.

DFG-Verfahren	Sachbeihilfen
Internationaler Bezug	Schweiz
Beteiligte Personen	Privatdozent Dr. Benno Graf Schimmelmann; Privatdozentin Dr. Frauke Schultze-Lutter