

Bilaga 2A - Research Program

Title: The pedagogic school environment, academic achievements, epigenetic mechanisms and mental health in early adolescence- A longitudinal study (KUPOL)

1. Specific objectives and aim of the proposed research program

1.1 Overarching aim

This research program sets out to assess the short-term effects of school environment on the mental health of adolescents. We will conduct a large scale longitudinal study, using surveys at the school, class, parent and student levels, information from Swedish health- and administrative registers, as well as biomarkers.

1.2 Primary objectives

The following core questions will be addressed:

1.2.1 Is school pedagogic environment and its specific dimensions (e.g. pedagogic leadership, teaching methods, relations in school) associated with the risk of mental ill-health and of psychiatric disorders in adolescence, and is this potential association moderated by gender?

1.2.2 To what extent is the potential relation between school pedagogic environment and mental health mediated by academic achievements?

1.2.3 Is school pedagogic environment associated with mental ill-health through modifications in the expression of genes, e.g. those regulating response to stress?

1.3 Additional objectives

The databases accrued within the frame of this project will allow further exploration of highly relevant areas, such as: feasibility and effectiveness of a screening for early detection of mental health problems among adolescents; costs of mental illness among school children; interaction between school- and family-level social and psycho-social factors and mental ill-health; effect of health-care interventions “as usual” on sub-clinical mental health problems.

2. Background

In adolescence, school is a key environment in which developmental milestones such as learning[1] and socialization[2] take place. Successful learning and academic achievements are the results of a complex set of determinants, related to the student him/herself, family, school environment, and teacher as well as the teaching style, and subject curricula[3]. Besides a recognized association between academic achievement and child/youth mental health[4] school performance seems to be intimately linked to health in a lifelong perspective and changes in school performance can influence health into adulthood [5]. Recent Swedish studies among young adults also show exceptionally strong and graded negative associations between compulsory school leaving grades and suicide [6] as well as hospitalization due to self-inflicted injury [7]. Such associations were independent of parental social disadvantage, education and psychiatric history. School failure may be causally linked to mental ill-health via labor market exclusion or expectations of such exclusion, particularly in a modern information economy such as Sweden[8]. Another potential key mechanism is loss of self-esteem due to failure and resulting emotional distress [9]. However, there is also strong evidence for the reverse causal relationship between school performance and mental health, i.e. that internalizing and externalizing mental health problems may negatively influence academic achievement [4]. Finally, school failure and mental distress may share common determinants such as genetic factors, adverse perinatal events, childhood adversity and low

Bilaga 2A - Research Program

cognitive competence[4]. Because of the multiple pathways involved, a singular focus is sometimes placed on what children bring with them when they enter schools (e.g., children's social background) rather than on school environment or the complex interaction between multiple influences. As a consequence, the relation between school pedagogic environment and mental health is insufficiently investigated, particularly in Sweden [4]. Such knowledge is greatly needed since there is evidence of increasing rates of internalized problems, especially in older teenage girls and young adults from the 1980s until today [10] [11], and in the light of current debates about the pedagogic principles of the Swedish school system.

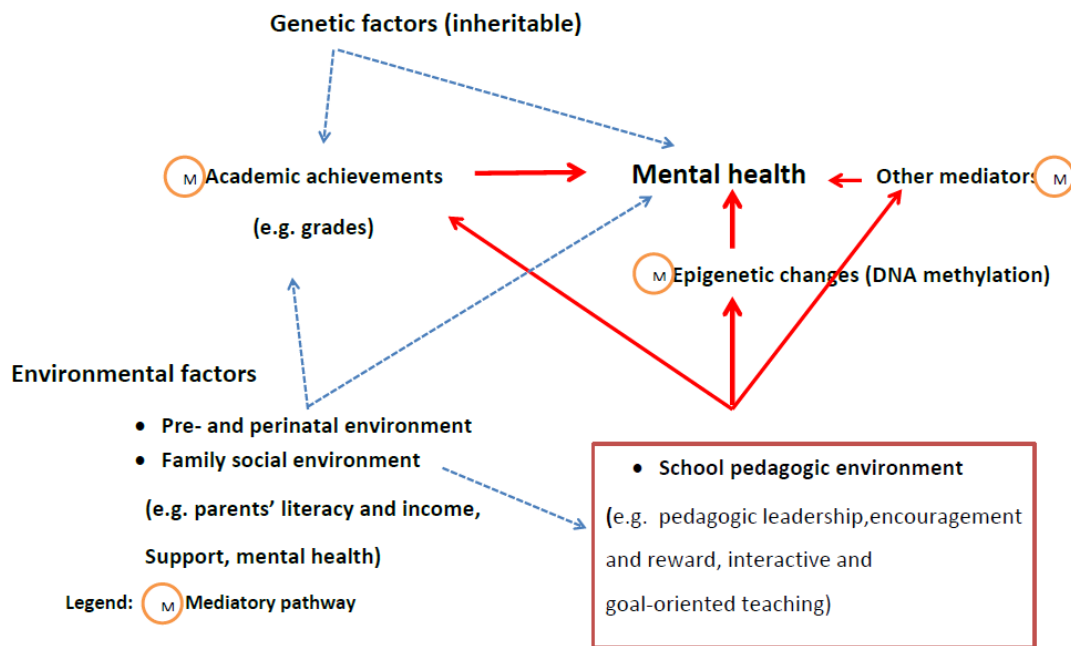
Considering the evidence for a meaningful connection between the ecology of schools, mental health, and achievement, some studies have shown that academic progress and indicators of adjustment – like disruptive classroom behavior – significantly vary at the school-building level above and beyond the contribution made by individual and family level factors [12]. Other studies have shown that aspects of schools, such as poor school climate, can act as risk factors for youth mental health, but also as protective factors that mitigate the influence of other individual level risks [13]. In an American short-term longitudinal study early/middle adolescents who perceived friction in their schools were more likely to experience internalizing and externalizing problems a year later [14]. In another study, the school social climate was found to work as a protective factor that buffered the effects of individual level risks (e.g., destructive forms of self-criticism) on later internalizing and externalizing problems [15]. The function of school climate as a risk or protective factor is likely connected to how school climate is variably conceptualized and measured across studies [16, 17]. Due to differing conceptions of school climate it is also important to explore how specific aspects of this construct may relate to child/adolescent mental health. In particular, the roles of organizational as well as of educational factors, such as teaching methods, curriculum characteristics, assessments and evaluation system deserve attention [4].

We therefore aim to address questions on which specific aspects of a school environment may be strengthening or detrimental for adolescents' mental health.

We also hypothesize that school pedagogic environment may influence mental health through epigenetic mechanisms, i.e. the silencing/activation of gene transcription, involved in pathways of stress response. Stress and its neurobiological correlates, mediated primarily by cortisol released by the hypothalamic–pituitary–adrenal (HPA) axis, are substantially involved in the causation and development of depression and anxiety disorders [18]. Children exposed to stress are at increased risk for developing alteration in HPA functioning and mental ill-health[19]. It has been shown that the DNA methylation status can be changed by adverse childhood experiences (such as childhood maltreatment and parental stress). Such epigenetic modifications have particular importance because they can influence the developing person through-out the lifespan [20], providing evidence that environmental stress can be cemented in the genome through DNA methylation [21]. Specifically, we hypothesize that the stress originating from the school environment can influence the DNA methylation pattern and thereby the expression of stress-regulatory genes such as the HPA-axis regulator *NR3C1*, which in turn moderates the risk for mental ill-health of the exposed adolescents. For instance, stress in school environment may be triggered by academic competition processes leading to low social rank. The latter is associated with negative cognitions such as submissive behavior, entrapment (i.e. the belief that there is no way out of the present situation) and problems with attachment to peers [22, 23], which in turn may increase the risk for mental health problems [24]. The herewith proposed work will constitute the first study in this respect, with hypothesized associations between school environment, academic performance, epigenetics mechanisms and mental health schematically represented in figure 1.

Bilaga 2A - Research Program

Figure 1. Study hypotheses (solid lines) and alternative causal pathways of academic proficiency and mental health



3. Project description

We plan to conduct a cohort study of about 10,000 children attending the 7th grade in a sample of schools located in 8 regions of central Sweden: Stockholm, Södermanland, Uppsala, Västmanland, Gävleborg, Dalarna, Örebro and Värmland regions, with follow-up through grade 9 and outcome assessment up to one year after completion of the compulsory school. The choice of the target Counties is based on logistic criteria as well as on a scrutiny of the regional differences in proportion of psychiatric diagnoses in the Patient Register.

3.1 Enrolment of the study population

3.1.1 Schools

A complete list of all schools in the target regions, both publically and privately run, will be obtained by Statistics Sweden. Schools are eligible if they enlist at least 2 classes (or at least 50 students) in grade 7 and if teaching is carried on in Swedish as mother tongue. Schools meeting the inclusion criteria (estimated in approximately 600 in the target area) will be entered in a computerized register that will be progressively updated with the information collected for the purpose of this study. We estimate a school-level participation of about 50%, yielding a final sample of at least 250 schools. An expansion of the study area is planned in case the desired participation rate is not achieved.

Procedure: Schools will be initially contacted with a letter addressed to the principal, containing a brief description of the study's leadership, aim and procedures (Attachment 4A). This initial contact is set to lead to a school-based meeting where staff and representatives of students and parents will be invited. At this stage all schools, irrespective of participation, will be asked to provide information on specific structural and functional characteristics, to be used to describe the selection introduced in the final sample. Schools accepting to cooperate will further provide detailed information on functional and structural characteristics described in paragraph 3.2.1 below. Schools will also be asked to facilitate the contact with the families of students to be included in the study, by sending home the invitation letter.

Bilaga 2A - Research Program

Because of the need to achieve a close cooperation with the school personnel during the data collection we plan to create “mobile teams” in each region, visiting the schools in the initial phase of recruitment, in order to present the project and give a thorough demonstration of the instruments and methods of data collection. Meetings will be scheduled in advance, but the teams will be available during approximately one week, in order to strengthen the contacts with the cooperating schools and to start the process of collecting information. As an incentive to participate, schools will have the possibility to access a discussion forum on the study web-site with periodic expert support. Also, schools will be reimbursed for teachers’ and health care team’s effort devoted to the project.

3.1.2 Student sample

All students registered in the 7th grade in the school year corresponding to project year 2 will, after active parental consent, be eligible to participate. Exclusion criteria will include severe learning disabilities and poor comprehension of the Swedish language.

Procedure: First, a letter of invitation to participate, including contact information to the project team, will be forwarded by the school using the common channels for school-family communications (Attachment 4B). The students will receive corresponding information directly in schools (Attachment 4D). Subsequent contacts with families will be established directly by the study team, using not only ordinary and e-mail, but also telephone contacts and small-groups meeting at the class level. A complete description of the project, of the data collection and data use will be available to the guardians, if necessary also translated into the foreign languages most representative of the immigrant populations in the target school. Non-native guardians will also be given the opportunity to contact mother language health communicators to obtain detailed explanations during the stage of cohort recruitment.

Active consent from all guardians will be sought, separately for the different parts of data collection (Attachment 4C). The child’s personal identifier (National Personal Number), necessary to perform register record linkage and to organize the follow-up, will be obtained at this stage. The desirable sample of 10,000 participants will be attained assuming the school level participation referred to above, an average of 70 eligible students per school and a 60% participation rate at the student level, estimates that we base on prior experience. [25]

Students’ participation will be rewarded with project-specific low-cost gadgets, such as stickers or pens with the project’s logo.

3.2 Data collection

We will employ a multi-level and multi-method data collection as described in details below, with surveys at the school, class, family, and student level. Both paper- and web-based instruments will be used. Self-reports will be complemented via record-linkages to national and regional health and administrative registers.

3.2.1 Measurement of primary exposure and other school characteristics

Teacher and student perception of the culture, climate and ethos of schools can be formally investigated and combined in a score denominated PESOC (Pedagogical and Social Climate of a school, <http://web.ped.su.se/PESOK/>). Factors that have been associated to a high PESOC score (i.e. most effective schools) in previous studies are, among others: clear and strong pedagogic leadership, teachers’ participation and cooperation, high expectation about students’ achievements combined with encouragement and reward for students’ performance, clear norms and sanctions, flexibility and interactivity of teaching, regular contacts between school and families [26].

Bilaga 2A - Research Program

The information constituting the base for the calculation of the PESOC score can be collected both as a paper-and pencil- instrument and through an internet-based instrument that has been used in previous studies (Attachments 5B and 5C). [27, 28] The instrument for teachers consists of a questionnaire containing 95 statements, while the instrument for students contains 57 statements. The statements refer to 13 factors among those associated with an effective school environment listed above. Agreement with the statements is given using a four-point Likert scale. The instrument has been tested by the Department of Statistics at Stockholm University and found to be highly reliable [29], therefore representing a promising tool in this research program. We will further test the psychometric properties of the instrument in a pilot phase of the study (described below in paragraph 3.4), which will possibly lead to a shortening of the instrument.

Procedure: All teaching personnel in the selected schools will be eligible for the PESOC survey. Among students, only those attending the 9th grade will be eligible, because they have the longest experience of the school as an organization. In other words, with exception for the last year in school, the ecological measure PESOC will not be based on information from the study cohort, making the assessment of the primary exposure independent from that of the outcome. Parental informed consent will not be needed for the PESOC assessment, since student ratings will be anonymous and will not encompass personal information. Students will be asked to complete the questionnaire in paper during an ordinary class session. Teachers will have access to both paper and electronic versions of the questionnaire. At baseline, information relative to other structural and organizational characteristics of the school will be collected by the principal, in particular concerning the personnel, their qualifications and professional development, as well as turn-over during the past year; forms of students' and families' participation; written policies and rules (e.g. concerning substance use, mobbing); common educational programs targeting behavioral and psycho-social risk factors (Attachment 5A).

3.2.2 Measurement of primary and secondary outcomes

The primary outcome, mental ill-health will be primarily assessed by means of multi-informant (teacher, parent, child) completion of the 25-item Strengths and Difficulties Questionnaire (SDQ). The SDQ is widely used, including in Sweden [30], and constitutes a valid instrument for screening of child mental disorders in community samples [31, 32] that is short, fast to complete (less than 30 minutes) and generates dimensional measures of mental ill-health. Multi-informant SDQ data can be used to predict psychiatric disorders fairly well [31]. The items are divided into five scales with five items each: Hyperactivity-Inattention, Emotional Symptoms, Conduct Problems, Peer Problems and Prosocial Behavior. The SDQ will be administered at baseline, at the beginning of each school year during the remaining compulsory grades and in the fall of year 5, at the transition towards the upper education. In order to increase the validity of the outcome assessment in the domain of internalizing problems the Center for Epidemiologic Studies Depression Scale for Children (CES-DC) [33], a 20-item instrument extensively used in population surveys and validated in Sweden [34] will be also administered.

Procedure: In order to avoid an excessive workload for teachers, we will use only parent and child assessments. The SDQ will provide a first-step screening assessment. Consenting families will be mailed the parent instrument at home, incorporated in a wider family assessment questionnaire (see 3.2.3) (Attachment 5E). The student instruments (SDQ and CES-DC) will be incorporated in a comprehensive questionnaire (Attachment 5D) where also other information (see 3.2.3) will be included. At each assessment, children scoring above the 90th percentile in some or all mental problem dimensions covered by SDQ will be considered as “probable cases” of any mental disorder in the present study. Newly detected cases will

Bilaga 2A - Research Program

therefore be referred to further assessments. During compulsory grades the results of the SDQ and of the CES-DC assessments will be communicated to the parents and simultaneously to the Health Care Team in the school. The latter will arrange the subsequent steps, which may go from simple surveillance to referral to the Child Psychiatric Unit of the residence area. During the out-of-school assessment the results of the SDQ will be communicated to the family of the index subject, with contact information to the Child Psychiatric Unit for further diagnostic procedure.

Subsequently, an attempt will be made to collect information on specific psychiatric diagnoses from computerized medical registers. In the Stockholm County this can be easily achieved through record link with a child and adolescent psychiatric service register with diagnostic information based on ICD-10, known under the name of "Pastill". A definite assessment of the feasibility of a similar procedure in other Counties will be part of the preparatory work during year 1 of the present study. In alternative, contacts will be established once per year with all Clinics in the schools' catchment areas in order to obtain information on possible neuropsychiatric diagnoses regarding participating students

3.2.3 Other socio-demographic and psycho-social factors

In order to control for potential confounding factors, to study mediatory as well as interaction effects, further data will be collected at the level of the class, family and individual student, at baseline and/or during each year of follow-up.

Class-level factors will be elicited in a structured interview to responsible teachers or mentors, and will include questions partially similar to those asked for the whole school, such as include: number of students; formal competence of the teachers in the core subjects; curricular activities for each core subject; cross-disciplinary and special pedagogic activities. Part of the interview will concern the social climate in the class, i.e. perception of discipline/absenteeism; the quality of relations among students, between students and teachers, and among teachers.

Family level factors will be elicited both through a structured parental questionnaire (Attachment 5E) and through register-based information. The parental questionnaire includes questions on composition of the family and the index child's cohabitation forms; parental employment and income; attitudes and expectations towards school achievements; bonding within family; guardians' own use of alcohol and tobacco. Register based information will encompass parental history of somatic and psychiatric disorders, to be obtained through registers held by the National Board of Health and Welfare (NBHW, the National Patient Register and Prescribed Drug Register); maternal morbidity, medications and use of tobacco during pregnancy through the Medical Birth Register (NBHW); parental leave, disability pension and other sickness benefits via the Swedish Social Insurance Register; parental socioeconomic factors (country of birth and year of immigration, employment status, occupational class, level of education, family disposable income and receipt of social subsidies) via the Integrated Database for Labour Market Research at Statistics Sweden.

Child-level factors will also be elicited both through a structured questionnaire (Attachment 5D) and register linkages. Besides the child SDQ and the CES-DC scales mentioned in paragraph 3.2.2 the questionnaire will include items on bonding to parents and peers; lifetime and recent use of tobacco, alcohol and illicit drugs; height and weight; and self-rated health, school orientation. Register-based information will include, in addition to outcome data described in paragraph 3.2.2: hospital admissions because of neuro-psychiatric illnesses and prescription of psychotropic drugs Welfare (NBHW, the National Patient Register and Prescribed Drug Register; days of unjustified school absenteeism (truancy) from school

Bilaga 2A - Research Program

registers; and academic grades in 6th and 9th grade (via the National School Register at the Swedish National Agency for Education); birth weight, fetal growth, gestational age and Apgar score (via the Medical Birth Register at NHBW).

3.2.4 Biological samples and study of epigenetics

With support from the school nurses we will collect saliva from a nested random sample of about 2000 consenting students at baseline (7th grade) and again at the end of the 9th grade. The student will be asked to spit in an Oragene tube (Oragene-DNA, DNA Genotek Inc., Ottawa, Ontario, Canada) for later DNA extraction, an Oragene tube for RNA extraction, and to chew for one minute on a soft piston for cortisol measurement (Salivette-Cortisol, Sarstedt). The cortisol sampling will be repeated twice, before the first lesson in the morning, and before leaving school in the afternoon. The nurse will estimate the pubertal stage of each student (pre-pubertal, early pubertal, late pubertal) and record their height and weight. All samples will be labeled with the child's study code and finally stored in the Karolinska University Hospital Biobank, after a delivery procedure involving the regional biobanks in the regions to which the schools belong.

Diurnal cortisol levels will be assessed by routine methods in clinical laboratory. Methylation of the DNA will be assessed using bisulphite treatment and subsequent quantification of methylation applying the Pyrosequencing PyroMark Q24 platform (Qiagen) or the EpiTYPER platform (Sequenom). The DNA-methylation analysis will be carried out at Center for Molecular Medicine (Lavebratt lab, Ekström lab), and at NOVUM, KI. Candidate genes of particular interest will be those previously reported to have variations in DNA methylation in regulatory regions that associate to mental ill-health and / or to childhood/adolescence adversities, such as the *glucocorticoid receptor NR3C1*, *monoamine-oxidase A (MAOA)*, the *serotonin transporter (5-HTT)*, *brain derived neurotrophic factor (BDNF)* and the *arginine vasopressin (AVPR)* genes. Whether an identified DNA methylation difference affects the gene expression will be determined using RNA. However, the funding plan for the RNA collection and analyses is not part of the present application, and will be pursued by means of other grants.

In a case-control design nested in the cohort we will compare students with SDQ-based mental ill-health, separately for those with or without abnormal diurnal cortisol pattern, to those students with normal mental health and normal cortisol level pattern. DNA methylation, child-level factors and family level factors will be studied as mediators of the relationship between school pedagogic environment (PESOC) and the outcome (SDQ and diurnal cortisol pattern). The relationship will be studied cross-sectionally, i.e. in the 7th grade and in the 9th grade, as well as longitudinally with predictors from 7th grade (mediators and PESOC) and SDQ/cortisol from 9th grade. Based on a conservative estimate of about 10% cumulative incidence rate during 2 years [35], we expect to include at least 150 children with mental disorders, individually matched on gender and pubertal stage to two controls.

3.3 Statistical methods

3.3.1 Statistical power

The proposed sample will provide 80% power to detect as statistically significant ($\alpha=0.05$) a 30% increase in the risk of mental health problems among students exposed to the lowest quartile of low PESOC score compared higher quartiles assuming a cumulative incidence among the unexposed as low as 8%, taking into account the cluster design. In the

Bilaga 2A - Research Program

case-control study of DNA methylation analyses, we expect to have a power of >80% to detect absolute methylation level differences of a few percent. The detection of smaller differences may not be biologically relevant.

3.3.2 Statistical analysis

Because the accrued data will have an inherent hierarchical structure, with students grouped in classes and schools, multilevel regression modeling will be the elective analytical method [36]. Both the primary outcome (SDQ-based mental health problems) and most secondary outcomes (e.g. substance abuse, conduct disorders, internalizing symptoms) will be primarily categorized as dichotomous. Therefore, we will use logistic regression to model yearly and cumulative incidence. The primary exposure (PESOC) will be analyzed as a continuous as well as a categorical variable. In the main analysis we will explore the mediatory and effect-modifying role of school proficiency, other individual-level factors (above all, gender) and out-of-school factors (e.g. family circumstances) on the association between overall school pedagogic climate, its sub-dimensions and occurrence of mental disorders. Potential confounders to be adjusted for mainly consist of familial social circumstances such as migration status and social adversity, which may indeed impact on choice of school as well as mental health [37]. Given the complex interplay of causal and non-causal relations occurring between different levels of environmental and individual factors the primary analyses will be complemented with alternative estimation and testing techniques, such as structural equation modeling [38].

Finally, conditional logistic regression will be used to analyze the case-control study of DNA methylation and cortisol levels.

3.4 Pilot study

In order to test the study instruments and procedures *a pilot study* will be conducted in at least 10 schools during the spring term 2013. Schools in the pilot study will be selected strategically to reflect the various settings expected in the main study, and will not be selected again for the main study. Trained research assistants will collect data from the students and perform classroom observations. Processes to be studied will be the efficiency of procedures for recruitment, parental compliance and feasibility of measurements. All information in the pilot study will be handled anonymously. In brief: the sequential code use to identify children in the class lists will be used to label all study instruments, thus ensuring the link for instance between parents' and children's data. The correspondence between individual student and code will be kept by the class teacher.

The test of *procedures for recruitment* will concern information for school principal, to staff, and to parents and students. Acceptance and comprehension of written documents (e.g. invitation letters) as well as of alternative information settings (e.g. meetings, help desk, web-site) will be explored through focus groups and structured interviews with key people in schools and randomly selected parents and students. *Parents' propensity to participation* will be studied by simulating informed consent procedures as close as possible to those to be employed in the main study. Particular attention will be devoted to understanding the role of barriers due to language and cultural diversity. *Measurement* issues to be addressed will concern:

- a. Collection of saliva samples by school nurses, with bogus sampling of 20-25 students per school. Main issues: students' acceptance of the procedure and the estimation of the nurses' work-load
- b. Administration of the SDQ instrument to parents and students. Main issues: respondent group's compliance and average time required to answer the instrument

Bilaga 2A - Research Program

c. Administration of PESOC to assess the school pedagogic climate. Main issues: teacher and student compliance. Further, the psychometric properties of the instrument will be explored in advance (pre-pilot during fall 2012). Further, an *observational setting* in usual teaching conditions will be arranged in about 10 randomly chosen classes, in order to validate information on teaching style and class social interactions reported by teachers.

4. Research team, projects' leadership and organization: The project will be based at the Karolinska Institutet, Department of Public Health Sciences and will involve a gender-balanced and inter-disciplinary group of researchers from Stockholm University, Uppsala University and Mälardalens högskola. Expertise in school-based longitudinal studies, psychiatric epidemiology, social epidemiology, pedagogy, psychology, genetics and health economics is represented. In particular, the main applicant has conducted major studies involving the recruitment of students in compulsory schools, including a longitudinal study [25] and an international cluster randomized study of substance use prevention[39]. Two young researchers in post-doc positions will be recruited into the project, with background in epidemiology and molecular genetics, respectively.

Informational tools and retention strategies will be crucial for the success of the proposed research. Therefore, we plan to launch a study-dedicated website, where information on the study's development and results will be continuously updated. Password-protected sub-domains to be accessed only by participant schools and families will not only allow online downloading and/or completion of some assessment instruments, but also participation in a discussion forum, with exchange of technical information and expert support.

5. Timeline and plan for scientific deliverables

The timeline of the study activities during the first three years is schematically represented in figure 2. We plan to conduct preparatory work, including the pilot study for development and testing of study instruments during year 1 and part of year 2. Field activities for the recruitment and follow-up of the study cohort and corresponding data collection will be conducted during years 2 to 5. Scientific articles with focus on methodological and descriptive aspects can be delivered already during year 3. However, the bulk of the scientific production will be concentrated during years 4 to 6.

6. Societal value of the research

Mental ill-health is a key contributor to the global burden of disease among youths. [40] This project aims to provide decision makers with empirical evidence linking the triad of school environment -academic achievements- mental health, a central question in the often inflamed political debate on what constitutes an optimal school environment to both foster children's knowledge and well-being. In Sweden, where important changes in compulsory education are advocated and expected in the coming years, there is a clear need for a large longitudinal study tackling school pedagogic environment in relation to children's mental health. As a spin-off, the study will offer important insights on feasibility, costs and effectiveness of a school-based screening for adolescent mental health problems.

7. Plan for communication with stakeholders and end-users

School management, teachers, students and their families will be clear end-users and beneficiaries of the advancement in knowledge expected from the research program. This should be true both on in a narrow (study participants) and in a broader sense, nation-wide. Therefore, the ambitious aim of the program is to provide with usable information decision-makers in the health-, the educational and ultimately the political arena. To this end, we will use both horizontal and vertical diffusion strategies, relying primarily on the study web-site and the Steering Committee (SC) described in paragraph 4. In particular, one important role

Bilaga 2A - Research Program

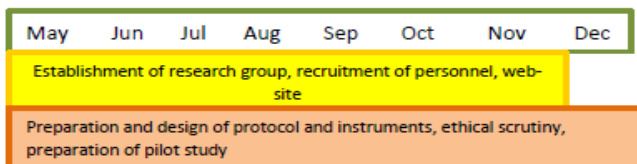
of the SC will be to facilitate consensus in the interpretation of the results and to set the agenda for the diffusion of information to the broader public. At the end of the first triennial period and once a year thereafter, open workshops will be organized with national and international researchers, as well as qualified representatives of public authorities, in order to discuss significance and implications of the research findings.

8. Scientific collaborations

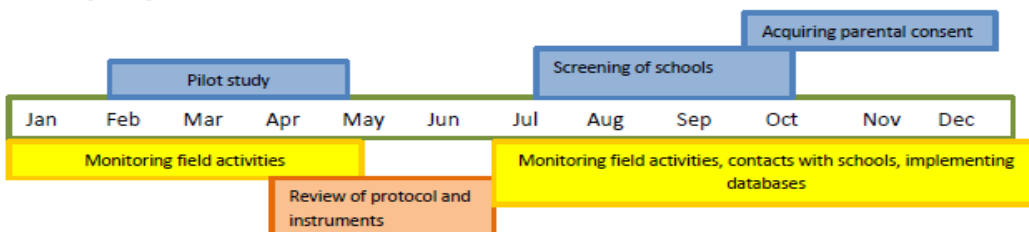
An international panel will be set up for the expert review of the study design and instruments. Beside Swedish scientists we plan to include educational scientists from the USA and the UK. Furthermore, collaboration with Bristol University (Professors Glyn Lewis and Jean Golding) which hosts the Avon Longitudinal Study of Parents and Children (ALSPAC) (<http://www.bristol.ac.uk/alspac/>), has been set up, with the aim to conduct comparative studies of school environment and mental health, contrasting UK adolescents in the 1990ies and 00ies to Swedish adolescents in the 2010ies.

Figure 2 Three-year timeline of the research program

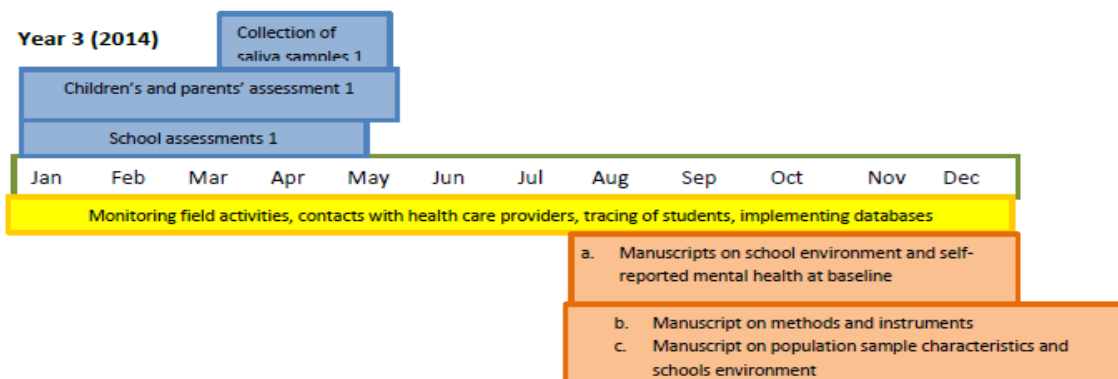
Year 1 (2012)



Year 2 (2013)



Year 3 (2014)



Bilaga 2A - Research Program

9. Ethical considerations

Ethical scrutiny will be sought before the project start. It should be underlined that the proposed research does not entail invasive or painful procedures. Active informed consent will be sought from the students' parents. Sensitive information will be handled without personal identifiers, only in order to obtain aggregated statistical measures. Furthermore, we intend to offer children whose values of psychometric scales deviate from the normal range a facilitated access to neuropsychiatric units for completion of the diagnostic process and treatment initiation, if needed.

10. References

1. Creed, P.A., J. Muller, and W. Patton, *Leaving high school: the influence and consequences for psychological well-being and career-related confidence*. *J Adolesc*, 2003. **26**(3): p. 295-311.
2. Van Ryzin, M.J., A.A. Gravely, and C.J. Roseth, *Autonomy, belongingness, and engagement in school as contributors to adolescent psychological well-being*. *J Youth Adolesc*, 2009. **38**(1): p. 1-12.
3. Hattie, J.A.C., *Visible Learning: a synthesis of over 800 meta-analyses relating to achievement*. 2009, London, New York: Rutledge.
4. Gustafsson, J.-E.A., M. Westling, Alin Akerman, B. Eriksson, C. Fischbein, S. Granlund, M. Gustafsson, P. Ljungdahl, S. Ogden, T. Persson, R.S., *School, learning and mental health. A systematic review.*, T.R.S.A.o.S.-H. Committee, Editor. 2010: Stockholm.
5. Fiscella, K. and H. Kitzman, *Disparities in academic achievement and health: the intersection of child education and health policy*. *Pediatrics*, 2009. **123**(3): p. 1073-80.
6. Bjorkenstam, E., et al., *Juvenile delinquency, social background and suicide--a Swedish national cohort study of 992 881 young adults*. *Int J Epidemiol*, 2011. **40**(6): p. 1585-1592.
7. Jablonska, B., et al., *School performance and hospital admissions due to self-inflicted injury: a Swedish national cohort study*. *Int J Epidemiol*, 2009. **38**(5): p. 1334-41.
8. Lager, A.C. and S.G. Bremberg, *Association between labour market trends and trends in young people's mental health in ten European countries 1983-2005*. *BMC Public Health*, 2009. **9**: p. 325.
9. Cole, D.A., *Preliminary support for a competency-based model of depression in children*. *J Abnorm Psychol*, 1991. **100**(2): p. 181-90.
10. Petersen, S.B., E. Cederblad, M. Ivarsson, A. Köhler, L. Rydell, A-M. Stenbeck, M. Sundelin, C. Hägglöf, B., *Barns och ungdomars psykiska hälsa i Sverige. En systematisk litteraturoversikt med tonvikt på förändringar över tid*, H. Kungl. Vetenskapsakademien, Editor. 2010: Stockholm.
11. Kosidou, K., et al., *Recent time trends in levels of self-reported anxiety, mental health service use and suicidal behaviour in Stockholm*. *Acta Psychiatr Scand*, 2010. **122**(1): p. 47-55.
12. Rutter, M. and B. Maughan, *School effectiveness findings 1979-2002*. *Journal of School Psychology*, 2002. **40**(6): p. 451-475.
13. Eccles, J.S. and R.W. Roeser, *Schools as developmental contexts during adolescence*. *Journal of Research on Adolescence*, 2011. **21**(1): p. 225-241.
14. Loukas, A. and J.L. Murphy, *Middle school student perceptions of school climate: Examining protective functions on subsequent adjustment problems*. *Journal of School Psychology*, 2007. **45**: p. 293-309.
15. Kuperminc, G.P., B.J. Leadbeater, and S.J. Blatt, *School social climate and individual differences in vulnerability to psychopathology among middle school students*. *Journal of School Psychology*, 2001. **39**: p. 141-159.
16. Kasen, S., J. Johnson, and P. Cohen, *The Impact of School Emotional Climate on Student Psychopathology*. *Journal of Abnormal Child Psychology*, 1990. **18**(2): p. 165-177.

Bilaga 2A - Research Program

17. Loukas, A. and S. Robinson, *Examining the moderating role of perceived school climate in early adolescent adjustment*. Journal of Research on Adolescence, 2004. **14**(2): p. 209-233.
18. Heim, C. and C.B. Nemeroff, *The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies*. Biol Psychiatry, 2001. **49**(12): p. 1023-39.
19. Trickett, P.K., et al., *Child Maltreatment and Adolescent Development*. Journal of Research on Adolescence, 2011. **21**(1): p. 3-20.
20. McGowan, P.O., et al., *Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse*. Nat Neurosci, 2009. **12**(3): p. 342-8.
21. McGowan, P.O. and M. Szyf, *The epigenetics of social adversity in early life: implications for mental health outcomes*. Neurobiol Dis, 2010. **39**(1): p. 66-72.
22. Wood, A.M., et al., *An evolutionary based social rank explanation of why low income predicts mental distress: A 17 year cohort study of 30,000 people*. J Affect Disord, 2011.
23. Gilbert, P. and S. Allan, *The role of defeat and entrapment (arrested flight) in depression: an exploration of an evolutionary view*. Psychol Med, 1998. **28**(3): p. 585-98.
24. Taylor, P.J., et al., *The role of defeat and entrapment in depression, anxiety, and suicide*. Psychol Bull, 2011. **137**(3): p. 391-420.
25. Post, A., M.R. Galanti, and H. Gilljam, *School and family participation in a longitudinal study of tobacco use: some methodological notes*. Eur J Public Health, 2003. **13**(1): p. 75
- 76.
26. Grosin, L., *Rektorer i effektiva skolor*. Nordisk Pedagogik, 2002. **22**(3): p. 158-175.
27. Grosin, L., *Skolklimat, prestationer och social anpassning i 21 mellanstadie- och 20 högstadieskolor.*, S. Universitet, Editor. 2004, Pedagogiska Institutionen: Stockholm.
28. McNamara, P., *The principal as change agent for school climate and pupil achievement*, in Department of Pedagogy. 1999, Stockholm University: Stockholm.
29. Carlson, M., *Reliabilitetsanalys av Bedömningsinstrument för Pedagogiskt och Socialt Klimat (PESOK) i skolor*. 2004, Department of Statistics, Stockholm University, Sweden: Stockholm.
30. Lundh, L.G., M. Wangby-Lundh, and J. Bjarehed, *Self-reported emotional and behavioral problems in Swedish 14 to 15-year-old adolescents: a study with the self-report version of the Strengths and Difficulties Questionnaire*. Scand J Psychol, 2008. **49**(6): p. 523-32.
31. Goodman, R., et al., *Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample*. Br J Psychiatry, 2000. **177**: p. 534-9.
32. Becker, A., et al., *Validation of the parent and teacher SDQ in a clinical sample*. Eur Child Adolesc Psychiatry, 2004. **13 Suppl 2**: p. II11-6.
33. Fendrich, M., M.M. Weissman, and V. Warner, *Screening for depressive disorder in children and adolescents: validating the Center for Epidemiologic Studies Depression Scale for Children*. Am J Epidemiol, 1990. **131**(3): p. 538-51.
34. Olsson, G. and A.L. von Knorring, *Depression among Swedish adolescents measured by the self-rating scale Center for Epidemiology Studies-Depression Child (CES-DC)*. Eur Child Adolesc Psychiatry, 1997. **6**(2): p. 81-7.
35. Bokedal, C., *Barns och ungdomars hälsa.*, S.l. landsting, Editor. 2010, Hälso- och sjukvårdsnämndens förvaltning: Stockholm.
36. Twisk, J.W.R., *Applied Multilevel Analysis*. 2006, Cambridge University Press: Cambridge.
37. Kosidou, K., et al., *Migration, school performance and current life circumstances in relation to psychological distress and suicide attempts among young adults*.
38. Anderson, J.C. and D.W. Gerbing, *Structural Equation Modeling in Practice - a Review and Recommended 2-Step Approach*. Psychological Bulletin, 1988. **103**(3): p. 411-423.
39. Faggiano, F., et al., *A cluster randomized controlled trial of school-based prevention of tobacco, alcohol and drug use: the EU-Dap design and study population*. Prev Med, 2007. **44**(2): p. 170-3.
40. Gore, F.M., et al., *Global burden of disease in young people aged 10-24 years: a systematic analysis*. Lancet, 2011. **377**(9783): p. 2093-102.

Bilaga 2A - Research Program