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To cite this article: S. Filatova, D. Gyllenberg, L. Sillanmäki, A. Suominen, S. Hinkka-Yli-Salomäki, A. Kaljonen, M. Kerkelä, M. Keski-Säntti, T. Ristikari, H. Lagström, T. Hurtig, J. Miettunen, H.-M. Surcel, J. Veijola, M. Gissler & A. Sourander (2019) The Finnish psychiatric birth cohort consortium (PSYCOHORTS) – content, plans and perspectives, *Nordic Journal of Psychiatry*, 73:6, 357-364, DOI: [10.1080/08039488.2019.1636135](https://doi.org/10.1080/08039488.2019.1636135)

To link to this article: <https://doi.org/10.1080/08039488.2019.1636135>



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Published online: 04 Jul 2019.



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The Finnish psychiatric birth cohort consortium (PSYCOHORTS) – content, plans and perspectives

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ABSTRACT

Background: Psychiatric disorders tend to be developmental, and longitudinal settings are required to examine predictors of psychiatric phenomena. Replicating and combining data and results from different birth cohorts, which are a source of reliable data, can make research even more valuable. The Finnish Psychiatric Birth Cohort Consortium (PSYCOHORTS) project combines birth cohorts in Finland.

Aim: The aim of this paper is to introduce content, plans and perspectives of the PSYCOHORTS project that brings together researchers from Finland. In addition, we illustrate an example of data harmonization using available data on causes of death.

Content: PSYCOHORTS includes eight Finnish birth cohorts. The project has several plans: to harmonize different data from birth cohorts, to incorporate biobanks into psychiatric birth cohort research, to apply multigenerational perspectives, to integrate longitudinal patterns of marginalization and inequality in mental health, and to utilize data in health economics research. Data on causes of death, originally obtained from Finnish Cause of Death register, were harmonized across the six birth cohorts using SAS macro facility.

Results: Harmonization of the cause of death data resulted in a total of 21,993 observations from 1965 to 2015. For example, the percentage of deaths due to suicide and the sequelae of intentional self-harm was 14% and alcohol-related diseases, including accidental poisoning by alcohol, was 13%.

Conclusions: PSYCOHORTS lays the foundation for complex examinations of psychiatric disorders that is based on compatible datasets, use of biobanks and multigenerational approach to risk factors, and extensive data on marginalization and inequality.

ARTICLE HISTORY

Received 12 December 2018

Revised 6 May 2019

Accepted 21 June 2019

KEYWORDS

Birth cohorts; consortium; data harmonization; psychiatry; causes of death

Introduction

Birth cohorts have had a significant impact on our understanding of the etiology of psychiatric disorders and are probably one of the best sources of reliable longitudinal data [1,2]. They have revealed that an individual's vulnerability to psychiatric disorders is affected by factors that affect neurodevelopment as early as the antenatal period [3] and that most psychiatric disorders emerge in childhood and adolescence [4–7]. Birth cohort studies have also demonstrated that the emergence of psychiatric disorders is affected by a broad range of social, developmental,

biological and genetic factors. Finally, multiple generations are a crucial aspect of psychiatric disorders [8–10]. Birth cohorts are, by their nature, multi-generational, as they include data from at least the mother and the offspring.

The Finnish Psychiatric Birth Cohort Consortium (PSYCOHORTS) comprises data from eight birth cohorts which can be linked through personal identification codes [11] to other national Finnish administrative health and welfare registers, as well as the current biobank legalization in Finland allows data linkages to sample data on mothers and their children. The project aims to harmonize different birth cohort data, incorporate biobanks into psychiatric birth

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 Supplemental data for this article is available online at [here](#).

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cohort research, apply multigenerational perspectives, integrate longitudinal patterns of marginalization and inequality in mental health, and utilize data in health economics research. The specific aims of this paper are to introduce content, plans and perspectives of the PSYCOHORTS project that brings together researchers from Turku, Helsinki and Oulu. Furthermore, we illustrate an example of data harmonization using available data on causes of death.

Content

The PSYCOHORTS consortium

The PSYCOHORTS consortium comprises eight birth cohorts. There are three prospective birth cohorts: the Northern Finland Birth Cohorts (NFBC) from 1966 and 1986 and the Finnish Birth Cohort (FBC) of 1981. There are also three register-based cohorts: the Finnish Birth Cohorts (FBC) of 1987 and 1997 and the Southwest Finland Birth Cohort (SFBC), which covered 2008–2010. Finally, there are two nested case-control cohorts: the selective serotonin reuptake inhibitors (SSRIs) cohort from 1996 to 2010 and the Finnish Prenatal Studies (FIPS), which provide data from nationwide research. By definition, a birth cohort consists of individuals born at a particular time, who are assigned to subgroups according to exposure status and followed up [12,13]. In nested case-control study designs, both the cases and controls are chosen from a defined cohort, for which some information on exposure and risk factor are already available [12]. Cohorts involved in the PSYCOHORTS consortium vary in lengths of follow-up periods, sample sizes and data collected (Table 1 and Table S1).

The Northern Finland Birth Cohort 1966 (NFBC1966), detailed at <http://www oulu.fi/nfbc/>, is one of the oldest prospective birth cohorts in the world. It aims to explore predictors of health and well-being at a population level. The prospective data collected from Northern Finland provides a unique resource that can be used for studies on the emergence of diseases, based on genetic, biological, social or behavioral risk factors. Biological samples including deoxyribonucleic acid (DNA) samples were collected when the cohort reached 31 years of age. There were still 7,043 participants when the last follow up was carried out at the age of 46–47 years, representing 58% of the original cohort. The NFBC1966 also includes extensive health and social register data. Psychiatric studies carried out using NFBC1966 data have included those on schizophrenia [14–17], depression [18], substance use [19] and criminal behavior [20,21]. In addition to the extensive clinical and survey data collected by the cohort, large amounts of genetic data are available for 5,401 members.

The Northern Finland Birth Cohort 1986 (NFBC1986), detailed at <http://www oulu.fi/nfbc/>, is a longitudinal one-year birth cohort study from an unselected population. Biological samples were collected in adolescence, when the subjects reached 15–16 years, and a comprehensive follow-up study will be conducted from 2019 to 2020 for all the remaining members of the cohort. In addition to extensive clinical and survey data, large amounts of genetic data are available for

around 4,000 members of the NFBC1986. Psychiatric studies using the NFBC1986 data have included studies on attention deficit-hyperactivity disorder [22–24], depression [25], psychosis risk and substance use [26–29].

The FBC1981 cohort consists of a nationwide sample of about 10% of the population [30], based on school sampling. Data on maternal health during pregnancy and delivery, neonatal events, developmental milestones and growth were collected from medical records. At the age of eight, 97% of the children in the cohort were assessed for psychiatric symptoms, bullying behavior and family-structure using questionnaires completed by the children and their parents and teachers. At the age of 18 years, the males in the FBC1981 study were assessed for psychiatric symptoms and sense of coherence using self-reports during military call up. The FBC1981 provides extensive register-based data on treatment for psychiatric disorders up to the age of 29 years, together with details on crimes, psychotropic medication use, abortions, teenage pregnancies and a family history of psychiatric disorders.

The FIPS provide data from nationwide research using a nested case-control design [31,32]. The data are based on linkages between a number of nationwide registers, namely the Medical Birth Register, the Care Register for Health Care, the Central Population Register, with additional background information from Statistics of Finland and the Finnish Maternity Cohort. The FIPS studies aim to examine the associations between several prenatal and perinatal risk factors and the development of psychiatric disorders. These include parental psychopathology, perinatal complications, indicators of fetal growth and development, smoking exposure during pregnancy, maternal exposure to infections and/or inflammation in pregnancy, parental age and parental socioeconomic status.

The 1987 Finnish Birth Cohort study (FBC1987) is a national, long-term, register-based, follow-up study that provides detailed information on various aspects of the health and social status of Finnish children born in 1987, along with their parents [33,34]. The unique strength of this cohort is that it provides a complete census of all infants born in a single year in Finland and subsequently followed through childhood to adulthood. The follow-up data are based on register information from administrative and population registers covering health, social welfare, education, employment and crimes. The data have been analyzed and their excellent quality has been confirmed [35–37].

The 1997 FBC is a continuation of the 1987 study and includes all children born in Finland in 1997. A recent study found increases in the incidence of psychiatric and neurodevelopmental disorders in the 1997 cohort compared to the 1987 cohort [38].

The SSRI cohort covers the years 1996–2010 and includes all children born to 15,729 mothers who purchased SSRIs during pregnancy. It also includes 9,651 mothers who had a psychiatric diagnosis but did not use antidepressants during pregnancy, 7,980 mothers who discontinued SSRIs before pregnancy and 31,394 mothers who did not take antidepressants or have a maternal psychiatric diagnosis. The age range

Table 1. Description and data sources linked with PSYCOHORTS.

Cohort	NFBC 1966	NFBC 1986	1981 FBC	FIPS ^a	1987 FBC	1997 FBC	SSRI exposure cohort	SFBC
N	12,231	9479	6014	N cases = 160,320 N controls = 618,847	59,476	58,802	N exposed = 15,700 N unexposed = 49,000	14,946
% of men	51	52	51	54	51	51	51	51
Year of baseline	1966	1986	1981	1983–2011	1987	1997	1996–2010	2008–2010
Follow-up (contact with participants)	At 14, 31 and 46 years	At 8, 16 upcoming at 32 years	At age 8 at age 18 (only men)	N/A	N/A	N/A	N/A	Continuously, currently until 6 years
The Medical Birth Register (STAKES)	+ for the offspring	+ for the offspring	+ for the offspring	+	+	+	+	+
The Register of Congenital Malformations (STAKES)	-	-	-	+	-	-	+	-
The Maternity Cohort and the Prenatal Serology Laboratory	N/A	-	-	+	p	p	-	+
The Central Population Register	+	+	+	+	+	+	+	+
Child Health Clinics	+	+	+	+	-	-	-	+
National Agency for Education	+	+	-	p	+	+	-	+
Care register for Health Care (STAKES)	+	+	+	+	+	+	+	N/A
Social Insurance Institution register ^b	+	+	+	p	+	+	+	+
The Legal register and police register	-	-	+	+	+	+	-	-
Ministry of Economic Affairs and Employment	-	-	-	-	+	p	-	-
Defence Forces	+	+	+	+	+	-	-	-
Center for Pensions (FCP)	+	+	N/A	-	+	+	-	N/A
Causes of death register (Statistics Finland)	+	+	+	+	+	+	+	+

^aData vary by sub-study.

^bInclude drug purchase, reimbursement of medicine expenses, and unemployment benefits.

FCP: Finnish Center for Pensions; STAKES: National Research and Development Center for Welfare and Health; +: yes (data available); -: no (data not available); N/A: non-applicable; p: planned.

of the children in this cohort is from birth to 14 years. The data were collected from the Drug Prescription Register, the Medical Birth Register, the Care Register for Health Care, the Register of Congenital Malformations and the Central Population Register [39–41].

The SFBC is a longitudinal birth cohort that consists of all children born in 2008–2010 in the Hospital District of Southwest Finland and their mothers. The cohort includes the STEPS study subsample, which has been previously described in more detail [28]. Information about the SFBC is based on pregnancy follow-up data from maternity clinics, national longitudinal census files and on-going data collection from child welfare clinics and school health clinics. The follow-up data on pregnancy from the maternity clinics include physical and mental health, maternal lifestyle habits, possible morbidity and early child and parent interactions. In Finland, child welfare clinics and school health clinics regularly follow the child's growth, health status, neurological and cognitive development and psychological and linguistic development. They also enquire about the parents' alcohol and smoking habits, and cover early interactions between the child and parent.

Additional clinical data has been gathered by some of the PSYCOHORTS studies. For example, some cohorts have administered psychometric questionnaires such as the Beck Depression Inventory or the Toronto Alexithymia Scale (Table S1). In addition, the two NFBC studies in 1966 and 1986, collected DNA and other biological samples [42].

Illustrating the data harmonization process using causes of death

The data harmonization process consisted of several stages. The process started by combining all the available metadata (a set of data that describes and gives information about other data) and variable level information from the birth cohorts into a single table.

We started by harmonizing the causes of death as this was the information that we needed to harmonize in the first instance. The necessary data dictionary and corresponding codebooks were created. The information on causes of death was obtained from the Finnish Causes of Death Register, which has been computerized since 1969 [43]. The causes of deaths were based on the International Classification of Diseases (ICD) codes covering the total study periods of the various cohorts: the eighth revision (ICD-8) covering 1969–1986, the ninth revision (ICD-9) covering 1987–1995 and the tenth revision (ICD-10), which has been used in Finland since 1996 [44]. By using the date of death we were able to identify the specific diagnostic system used and could specify the cause of death. They were presented as immediate, intermediate and underlying causes of death and included several variables. The underlying cause of death was considered to be the core variable.

Statistics Finland [45] provides a short list of 54 different categories of causes of death. Based on the ICD codes from the causes of death variable, we were able to create a similar list to our metadata. To do this, the statistics core at the

University of Turku programmed a macro in SAS software version 9.4 and applied by the other centers. Prior to adapting the original list from Statistics Finland to the macro some manual editing of the items in the original short list due to inconsistencies was done.

Results of causes of death harmonization

The raw data consisted of 22,149 causes of death for all cohort members and their parents when all the PSYCOHORTS birth cohorts were combined. The validation procedures confirmed that all the personal identification numbers were correct. However, we detected 156 duplicates of causes of death at the individual level. These duplicates were excluded, so that individual appear only once in a specific cohort. All the dates were complete between 2 October 1965 and 31 December 2015 (Figure S1). We found that 35 ICD-8 diagnoses had some additional characters, for example, an ampersand sign, but all the ICD-9 and ICD-10 diagnoses were presented in the correct format. After cleaning ICD-8 codes could be used as the other codes.

Only 326 (1.5%) deaths had missing diagnostic codes and this meant that we were able to process 21,993 causes of death. Several methodological challenges were encountered during the data harmonization process. For example, the classification list had some unclear inclusion and exclusion codes due to changes in coding practices for the cause of death register and diagnoses had different levels of accuracy and were not presented in a consistent way. Missing information on the month or day of death was checked, because these could have influenced the estimation of some psychiatric disorders that had seasonal or weekday patterns. However, no such cases were observed.

The mean age of the cohort members who died during the study period was 38.5 years. In the harmonized data, the overall number of deaths due to suicides and sequelae of intentional self-harm was 3,092 (14%) and due to alcohol-related diseases, including accidental poisoning by alcohol was 2,840 (13%). The number of deaths from suicides and sequelae of intentional self-harm varied between the cohorts from 15 (0.1%) to 1,069 (4.9%) (Table 2). The number of deaths from alcohol related diseases and accidental

Table 2. Characteristics of age of death from suicide and intentional self-harm in PSYCOHORTS.

Cohort	N	Mean	Median	IQR	Min	Max
NFBC 1966 cohort members	111	32.2	31.1	25.5–39.8	17.0	47.9
NFBC 1966 parents ^a	237	52.9	52.4	44.1–61.8	26.6	88.9
NFBC 1986 cohort members	36	22.9	24.0	20.3–25.8	25.6	18.0
NFBC 1986 parents ^a	153	43.7	45.0	37.0–49.5	24.8	67.9
FBC 1981 cohort members	26	23.2	23.1	19.8–26.6	15.3	31.4
FBC 1981 parents ^a	96	45.1	45.9	37.9–52.1	22.9	69.3
FBC 1987 cohort members	169	22.5	22.4	19.9–25.2	14.1	26.8
FBC 1987 parents ^a	702	42.7	42.9	36.6–48.8	20.4	69.3
FBC 1997 cohort members	15	16.3	16.2	15.9–17.3	11.4	18.6
FBC 1997 parents ^a	367	39.4	38.9	33.6–45.1	20.5	63.3
FIPS cohort members	111	19.2	19.0	17.5–21.0	11.9	25.6
FIPS parents ^a	1069	40.8	40.5	34.3–47.0	20.5	74.4

^aParents of cohort members. IQR: interquartile range.

Table 3. Characteristics of age of death from alcohol-related diseases and accidental poisoning in PSYCOHORTS.

Cohort	N	Mean	Median	IQR	Min	Max
NFBC 1966 cohort members	54	42.3	43.0	39.1–46.4	28.4	49.2
NFBC 1966 parents ^a	250	58.0	60.1	51.2–65.9	28.9	81.3
NFBC 1986 cohort members	2	30.0	28.0	27.0–29.0	27.0	29.0
NFBC 1986 parents ^a	122	51.7	51.7	45.6–56.9	32.0	75.1
FBC 1981 cohort members	4	29.8	29.6	27.1–32.6	26.6	33.5
FBC 1981 parents ^a	143	51.9	53.0	47.5–57.5	31.8	67.0
FBC 1987 cohort members	19	22.4	23.1	21.1–25.5	2.6	28.8
FBC 1987 parents ^a	868	49.3	49.7	44.3–54.0	28.6	73.9
FBC 1997 cohort members	0	–	–	–	–	–
FBC 1997 parents ^a	297	46.6	46.5	42.4–51.1	24.52	64.9
FIPS cohort members	9	20.2	21.4	20.5–23.6	2.7	26.2
FIPS parents ^a	1072	47.5	47.5	42.2–52.8	23.3	77.0

^aParents of cohort members. IQR: interquartile range.

poisoning by alcohol varied from 2 (0.0%) to 1,072 (4.9%) between the cohorts (Table 3).

Discussion

The PSYCOHORTS will create exceptional opportunities to answer key questions about etiology, risk and resilience factors and long-term outcomes of psychiatric problems. Through data harmonization we will be able to achieve more interaction between cohorts and large study samples that are needed to produce replicable results. With extensive available data on biological markers, health, psychosocial wellbeing, social welfare, and academic and occupational achievement, we will be able to better comprehend individual patterns of psychiatric diseases' development and related to them marginalization and inequality. Based on this information experts in health economics and administration will be able to tackle current challenges in individual and population healthcare, such as treatment interventions, societal change and geographical and health inequalities

Plans and perspectives of PSYCOHORTS

PSYCOHORTS combines the major prospectively designed Finnish psychiatric birth cohorts and first plan is to harmonize the data that these provide. Integration and harmonization of data from different cohorts allows better generalizability and comparability of results [46,47]. The way that data are recorded in national registers in Finland provides us with the opportunity to link each birth cohort with a variety of registers [11]. Psychiatric diagnoses can be collected from several sources, such as data on hospital care in the Care Register for Health Care, data on health-related benefits from the registers of the Social Insurance Institution and data on work periods from the Center for Pensions. Furthermore, PSYCOHORTS provides prospectively collected birth cohort data on putative risk factors, from pregnancy or birth, for members of the general population born during a specific period. This prevents the methodological issues that can be encountered in cross-sectional, retrospective, high-risk studies or studies based on clinical samples [2]. Early life risk factors can be obtained from sources such as the Medical Birth Register or Central Population Register. Furthermore, data on psychopathology in childhood is

available, which is relatively rare [2]. Described data are possible candidates for integration. Data harmonization is a challenge and several limitations may emerge. For example, ethical issues may prevent data sharing and heterogeneity in cohorts may complicate data harmonization [48,49]. Despite these limitations, this is still a process that is needed and the data harmonization provided by PSYCOHORTS will result in the creation of large and unique epidemiological data that can be used to tackle many of the key problems in psychiatric research.

The second plan of the project was to utilize existing Finnish biobanks in the PSYCOHORTS consortium. Combining pure biological data from biobanks with large cohort data will help identify biomedical patterns that predict diagnosis and phenotypes with high accuracy, which is the major goal of personalized medicine [50].

The third plan was to form multi-generational data sets that would provide the possibility to use existing register data. Both genes and environmental factors play an important role in the aggregation of psychiatric disorders in families. In this approach, grandparents, parents and children are linked across generations by common genetic, but also by environmental influences.

The fourth plan was regarding integration of longitudinal patterns of marginalization and inequality in mental health. This consortium will help understand the accumulation and interaction of individual deficits in health and wellbeing as well as psychiatric illness as potential risk factors for marginalization in a framework of societal changes over a period of several decades.

Finally, PSYCOHORTS data can be utilized in health economics research. Combining several birth cohorts from different time periods makes it possible to analyze the changes in the impact of mental health problems on economic circumstances affecting adult health, education, employment and socioeconomic status. The use of time dimension data from combined cohorts will help understand the extent as well as the risk/protective factors on the economic impacts of mental illnesses.

The main strength of our consortium, as demonstrated by this study, was that we were able to combine different sources of data and carry out complementary examination of the same psychiatric phenomenon across a number of cohorts. It also can provide a more comprehensive picture of the development of psychiatric disorders and a better understanding of the trajectories of those developments than one just birth cohort would have provided [2]. Some limitations should be considered with regard to some of the register-based data, because it was originally collected primarily for administrative or clinical purposes and not with future research in mind [42]. First, some exposures and outcomes that were extracted from the registers might have been poorly defined in the administrative data and their simplified categorizations maybe less suitable for research purposes [11,51]. In addition, the clinical data provided by the birth cohorts tended to be more detailed, but were not necessarily available for all cohort members [42]. Second, only individuals with severe psychiatric disorders were included in most of the registers

[11], even though data on outpatient visits are now increasingly available. Third, the coverage of the registers may have differed by year and by the fact that information was not always available. Despite this, the possibility of using register-based data, combined with biological samples and questionnaires, to examine psychiatric disorders was a unique characteristic of the PSYCOHORTS consortium. In addition, the attrition rates varied between cohorts and can be expected to increase over time. For example, attrition rate in FBC 1987 was only 0.1% [34], but in oldest cohort NFBC 1966 with several follow-ups an attrition with respect to psychiatric scales increased from 24 to 39%. It was also found that individuals with any psychiatric disorder in NFBC 1966 were more likely not to participate compared to those without any psychiatric disorder [52]. Selective dropouts in cohort studies can result in biased estimates of the risk factors' effect on an outcome [53,54].

Causes of death harmonization

We chose causes of death data as a first harmonization target and this process resulted in us identifying 21,993 causes for further analysis. The causes of death were not available or not collected in the SSRI, SFBC and some of the FIPS studies. The harmonized data that we produced was of a good quality, as the autopsy rate was high in Finland and medical experts checked the coding regionally and at Statistics Finland [55]. However, there could be some misclassifications as data collected over long-time period and, therefore, might be affected by changes in coding practices. We chose to narrow down the data by focusing on mortality due to alcohol-related diseases and suicide, which were associated with psychiatric disorders [56,57]. These estimates suggested a need for a cross cohort examination to focus on psychiatric disorders and their etiology.

A limitation of the causes of death harmonization process was that some study subjects could have been members of more than one cohort. Although that number was probably not large, it should be analyzed in future research. The individuals in different cohorts could only be identified once they had provided informed consent. If consent acquired previously, linkage to register-based and biobank data do not require a new consent, but it is necessary when collecting new data by questionnaires or when collecting biological data. We noted that 326 causes of death codes were missing, but this number accounted for 1.5% of the total cohort and was regarded as relatively low.

Conclusions

This project highlights the importance of such initiative as it provides researchers with the opportunity to carry out large-scale and a holistic examination of psychiatric disorders. Integration of these cohorts will enable researchers to address issues related to the development, trajectories and life outcomes of psychiatric disorders.

Acknowledgments

We would like to thank data manager Juha-Pekka Virtanen for his contribution. We would like to thank all the INVEST investigators and participants for their helpful comments.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This research was funded by the Academy of Finland Flagship Program (decision number: 320162), the Strategic Research Council at the Academy of Finland (decision number: 303581) and the Academy of Finland Health from Cohorts and Biobanks Program (decision number: 308552). This research was supported by the INVEST Research Flagship, APEX Research Consortium and PSYCOHORTS consortium.

Notes on contributor

PhD S. Filatova prepared the draft of the paper and revised it. MSc L. Sillanmäki, MSc A. Suominen, MSc S. Hinkka-Yli-Salomäki, MSc A. Kaljonen, MSc M. Kerkelä, and MSc M. Keski-Säntti contributed with data harmonization and data description. PhD, Dr D Gyllenberg, PhD T Ristikari, Professor H. Lagström, PhD T. Hurthig, Professor J. Miettunen, PhD H.-M. Surcel, Professor J. Veijola, Professor M. Gissler and Professor A. Sourander contributed with a description of the content of PSYCOHORTS, planning and revision of the article.

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