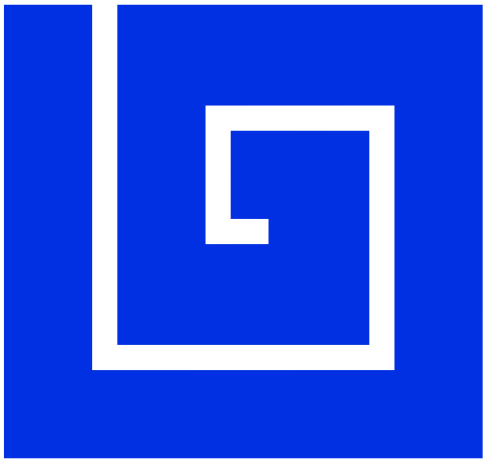
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EDITORIAL

TUULA KIESEPPÄ

Psychiatria Fennica 2026 goes back to the very basics of psychiatry. Our theme of the year is psychoses, and I am happy to present the volume with around half of the articles dealing with vivid ongoing psychosis research in Finland. The interest in psychoses was one of the leading causes for me to orientate to medicine. At that time, just after leaving school and planning my future, I had a great interest in the human mind, and my strong motivation to study medicine was to learn more about mental disorders. I found psychotic experience a fascinating although bewildering deviation from so-called normality, which, in my opinion, could offer a very special and deep view in what humanity is about. Here I refer to humanity as the human mind covering affect, intelligence, capability of language and self-reflection.

During my Ph.D. studies I came across papers by the psychiatrist and researcher Tim Crow (1,2), who passed away last year. He proposed an interesting idea that psychosis is a price that we humans must pay because of the ability of language related to lateral specification of the brain. Although the theory did not gain acceptance within mainstream psychiatry, it resonated with me intuitively. The basic phenomenon of psychosis is the difficulty to distinguish between real and unreal, between mental images and facts in outside reality, and this evidently seems to be linked to the human-specific ability of self-reflection and language. Language is not just a library of signs, but a bridge between our inner mind and physical reality, with a very complex symbolic system and network crabbing across different parts of the brain. When our mind-body system, for one reason or another, disintegrates or functions asynchronously, this manifests itself in fractures of self-reflection and language, possibly producing psychotic experiences.

Tim Crow was also among the first researchers to suggest substantial genetic background in schizophrenia. The ideas of aetiology of psychotic experiences and disorders have varied during history from mainly biological or psychological explanations to society-derived or even religion-based interpretations. Shared prevailing scientific view is that there are certain biological factors that contribute to the risk of psychosis, but both psychological and society-related causes in varying emphasis play a role. During recent years the high interest in research of psychoses has been in genetics. Although rare variants with high risk for psychosis and a large variety of variants with small or medium risks have both been detected, the complexity of the phenomenon remains. However, we have learnt a lot about the interaction between environment and genetics, including interaction between the psyche and biology. There is not one psychosis, and there is not one explanation.

Finnish mental health professionals and patients have contributed to the research of psychoses in many ways, which is explored in the exhaustive overview as an invited editorial of professor Jaana Suvisaari. Professor Suvisaari has been and is both an important collaborator and a principal investigator in numerous and varying national and international studies, and her expertise and knowledge covers a wide range of different study populations, study problems and study methods, which gives an extremely valuable frame for the overview and its conclusions. Also remarkable is that alongside internationally appreciated high-quality research studies, the Finnish research in psychoses has succeeded in offering data and knowledge to our public service system to develop more effective and qualified practices to fulfill patients' needs.

Besides research with psychoses, I have had the opportunity to work both as a psychiatrist and as a collaborator with people who have had psychotic disorders. These encounters and interactions have profoundly affected me as a doctor and human. I have deeply understood that even at its highest, certainty is only partial, and this is good to remember in all patient contacts. As a person, the right for autonomy is one of the most important values and targets, and we should foster this regardless of person's diagnosis or illness. In this volume I am especially grateful for the articles focusing on personal recovery (Tolonen Jonna; Kämäräinen et al.) and a psychiatrist's own experiences as a psychiatric patient (Sadeniemi Minna). We have, over a couple of years, discussed

with editors Jääskeläinen and Karukivi about the possibility to have a personal view article inspired by Schizophrenia Bulletin First Person Accounts, and now we can offer that. Importantly, Sadeniemi points out the stigma of psychiatric disorders, which has not disappeared despite all the talk about mental health.

Finally, I would like to thank all those patients who have shared their colourful, rich, although sometimes frightening inner lives with me. There is not one normal or one extraordinary lifestyle that should be goal for everyone. There are numerous ways to live a meaningful life, which we should learn from each other and appreciate. Last year's editorial I picked literature as a means to support better mental health and to bridge the gap between humans, and now I would like to recommend the delightfully strange and funny books of Leonora Carrington, who, as a young woman, was hospitalized because of a psychosis diagnosis. However, her later career as a fine artist and novelist was brilliant and productive. The novel The Hearing Trumpet (1974) and the children's book The Milk of Dreams (2013) are examples of ways to think differently, and to find humour in odd and dangerous places and times.

In Psychiatria Fennica 2026 we want to thank all the reviewers who made possible both volume 2025 and volume 2026 with their high-quality expertise, covering this time the very large scale of research areas from arts to social sciences alongside medicine, psychology and biology. We publish all the names of referees who have given their consent. Together with editors Jääskeläinen and Karukivi we would like to point to the exceptional enthusiasm and interest that the referees have shown.

Tuula Kieseppä
Editor-in-Chief, Psychiatria Fennica

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JAANA SUVISAARI

FINNISH RESEARCH ON PSYCHOTIC DISORDERS IN THE 2020s

KEYWORDS: PSYCHOTIC DISORDERS, SCHIZOPHRENIA, RESEARCH, FINLAND

Finland has had a strong position in psychosis research. Finnish cohort, general population, family, adoption and twin studies have been famous, as has been, for example, Finnish genetic and brain imaging research. This editorial discusses the present state of Finnish psychosis research and its main areas in the 2020s.

One PubMed search revealed that I do indeed have something to write home about. It would be impossible to provide a comprehensive description or list of publications. In the following, I aim to give a couple of good examples of different types of Finnish psychosis research.

Register-based research utilizing nationwide healthcare and other registers has been highly successful in all Nordic countries (Laugesen et al. 2021). In Finland, the most successful register-based research line in psychotic disorders has been pharmacoepidemiological research. Jari Tiihonen, Heidi Taipale and Antti Tanskanen have led this work and advanced the methodology of pharmacoepidemiological research. They have numerous publications from Finland in the 2020s related to antipsychotic medication treatment strategies (Taipale et al. 2025) and side effects (Luykx et al. 2024). In collaboration with Solja Niemelä and Swedish researchers, they have also investigated the treatment and longitudinal course of substance-induced psychotic disorders (Jeyapalan et al. 2026).

Data from several nationwide registers were combined to establish the Finnish Quality of Psychosis Care register, which publishes a variety of indicators on the treatment and outcomes of non-affective psychotic disorders. The main purpose of the quality register is to inform the wellbeing services counties of their performance in the treatment of psychotic disorders, and research is being done to deepen the understanding regarding results – for example, factors that have predicted rehospitalizations (Suokas et al. 2024).

Nationwide registers have also been used to form birth cohorts, which are then used to investigate risk factors or psychotic disorders. For example, adolescent mental health conditions and their treatment and subsequent risk of psychotic disorders have been studied by constructing a birth cohort from those born in Finland between 1987 and 1997, showing, for example, that SSRI medication did not protect adolescents with depression from subsequent psychotic disorder (Healy et al. 2025). Register-based birth cohort approach was also used to study whether and which school grades predicted later development of non-affective psychotic disorders (Gyllenberg et al. 2022). Adding register information on family members has allowed investigation of familial risk of psychotic disorders (Healy et al. 2024).

Register-based studies have investigated important outcomes, like employment (Ringbom et al. 2023) and mortality risk (Lieslehto et al. 2024). On the other hand, they have also been used to study specific risk factors like paediatric traumatic brain injury (Laaksonen et al. 2025), and specific outcomes like fatal motor vehicle accidents involving drivers with psychotic disorders (Koskinen et al. 2026).

Having biobank samples available adds precision to the investigation of risk factors. Andre Sourander, with Finnish and American researchers, has utilized the Finnish Maternity Cohort with serum samples available from the first and early second trimester of pregnancies. As an example, they studied maternal vitamin D levels, finding no association between maternal vitamin D levels in early pregnancy and offspring schizophrenia (Sourander et al. 2024).

Prospective Finnish cohort studies with repeated health examination or questionnaire-based assessments and linkage to register data produce important results on the risk factors of psychotic disorders. The Young Finns Study is one of them, finding, for example, that frequent stress-prone life events and disadvantageous emotional family atmosphere predicted higher likelihood of non-affective psychotic disorders (Saarinen et al. 2023). Investigation of psychotic disorders continues in the Northern Finland 1986 and 1966 birth cohorts, reporting, for

example, productivity costs of psychotic disorders (Majuri et al. 2024) and factors predicting progressive brain structural changes (Konttajärvi et al. 2024).

Finland continues to be at the forefront of genetic studies of psychotic disorders. A remarkable joint effort of all Finnish psychiatric university clinics is the SUPER study, a cohort of 10,403 individuals with psychotic disorders (Lähteenvuo et al. 2023). Both genetic (Kämpe et al. 2024) and numerous clinical (e.g. Mäkipelto et al. 2024) articles, as well as a combination of both (e.g. Cederlöf et al. 2025), have been published from this ongoing study. Pharmacogenetic research is also active in Finland (e.g. Rask et al. 2025).

A traditional, important research line in psychosis research is clinical cohort studies. One such cohort consists of a longitudinal follow-up of all adolescents treated at a psychiatric inpatient ward at Oulu University Hospital between April 2001 and March 2006. While 23% of these adolescents developed a schizophrenia spectrum disorder (SSD) during the 17 to 22-year follow-up, having subthreshold psychotic symptoms during the inpatient stay did not predict future SSD (Kieseppä et al. 2025). Longitudinal cohort studies on first-episode psychosis have been done at the Finnish Institute for Health and Welfare (e.g. Leijala et al. 2025) and at the University of Turku (e.g. Armio et al. 2024), in close collaboration in recent years with a focus on immunological mechanisms in psychotic disorders (Laurikainen et al. 2020, Rankka et al. 2025). In the longitudinal studies on psychosis risk and first-episode psychosis, University of Turku has also long-standing international collaboration (e.g. Plavén-Sigray et al. 2021, Neuner et al. 2025).

One famous line of psychosis research in Finland relates to brain imaging. Jarmo Hietala has led this line of research at the University of Turku, using both MRI (e.g. Tuominen et al. 2025) and PET methodologies (e.g. Borgan et al. 2021). MRI- and fMRI-based research has also been done at the University of Oulu (e.g. Lieslehto et al. 2021) and at the Aalto University (e.g. Hayward et al. 2023).

Forensic psychiatric psychosis research is active in Finland. Themes include for example the association of psychopathic traits with later risk of schizophrenia (Vaurio et al. 2025), crime recidivism after forensic psychiatric care (Sivak et all. 2025) and post-discharge mortality (Ojansuu et al. 2024).

Investigator-initiated clinical trials have been less common in Finnish psychosis research. Examples are a mobile therapeutic intervention for treatment-resistant schizophrenia (Seppälä et al. 2025), an ongoing trial on video gaming to improve functional and clinical outcomes in schizophrenia (Välimäki et al. 2026), an ongoing study on cognitive behavioural therapy for insomnia in schizophrenia and schizoaffective disorder (Tanskanen et al. 2024) and transcranial magnetic stimulation for treatment-refractory schizophrenia (Tuppurainen et al. 2024).

Important themes in psychosis-related research in recent years have also been, for example, expert-by-experience practices (Lumén et al. 2025), rehabilitation in assisted living services (Jahangiri et al. 2025) and factors that affect the implementation of physical health screening in mental health services (Långstedt et al. 2025).

This editorial is not an exhaustive list of Finnish psychosis research. It would have been impossible, given the impressive scope and breadth of research done in Finland. I mostly excluded basic research, although there would have been several excellent examples. My apologies to anyone who was not mentioned. My purpose was to illustrate that we do a lot.

Finnish psychosis researchers are good at leveraging our national strengths, such as nationwide healthcare registers and biobanks. We also have broad methodological expertise. However, I missed some themes. In my search from the most recent years, I did not come across a single validation study of different assessment methods. I have often wondered whether we are using the best possible instruments and assessment methods in clinical practice and research. What if we jointly decided which novel methods we want to adopt and conducted validation studies on them together?

What about psychosocial interventions, or other areas of treatment development? For example, should we aim to structure and improve inpatient treatment, and study the effectiveness of such efforts? Or should we develop and investigate services for people with long duration of illness? Currently, their treatment is often transferred to primary care, but what happens and what should happen after that? Could we carry out randomized multicentre trials together? In Denmark and the United Kingdom, this is constantly being done, and the results inform service development. These countries have more research funding available — but it is worthwhile to look, for example, at the large-scale surgical randomized clinical trials conducted in Finland. If it can be done in surgery, why couldn't we psychiatrists do the same?

It would also be excellent to see more Finnish clinical cohort studies – for example, longitudinal studies of first-episode psychosis patients. We have our nationwide registers, but with rather superficial information. Large language models will allow using patient record information in the future, but we lack harmonized measures and will not get biological samples without clinical research. Collaboration would allow studying a multitude of important research questions.

This editorial invites readers to explore the current issue of Psychiatria Fennica, which is dedicated to research on severe

mental disorders. It offers numerous examples of Finnish research in this field. I hope it helps bring together people with shared clinical or research interests and fosters future collaboration. We are already good — let us become even better together!

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MINNA SADENIEMI

UNRAVELLING STIGMA – A PSYCHIATRIST'S EXPERIENCE AS A PSYCHIATRIC PATIENT

KEYWORDS: BIPOLAR DISORDER, DOCTOR AS A PATIENT, EXPERT BY EXPERIENCE, STIGMA

When I studied medicine in the 1990s, it was never discussed what to do if a doctor became ill and needed medical care themselves. What I did learn was that medical doctors are at greater risk of suicide than other people with the same level of education. I recall learning that, compared with the general population, the relative suicide risk was especially high among female doctors, anaesthesiologists and psychiatrists. Not a single lecture during the six years of medical school addressed how to reduce the risk of ending up making that tragic final decision. Nor was it discussed how to cope with mistakes one makes, or with the responsibility, demanding working hours and chronic stress inherent in the medical profession. Nor did anyone talk about what to do if one needed psychiatric care as a doctor. We were never encouraged to seek help ourselves. It was never said aloud that it was okay to seek help when needed.

When I recently gave a lecture to young doctors specializing in psychiatry in Helsinki, I asked whether the situation had changed over the past 30 years. The answer was no. One young colleague said that the subject had once been mentioned by a professor during a lecture attended by about one hundred students. The lecturer had demonstrated the prevalence of serious mental disorders by explaining how many of the students present would eventually receive such a diagnosis. But then the professor added that, of course, this prevalence did not apply to them. Why not? Nobody dared to ask.

Why would being a medical professional protect someone from psychiatric illness? Is the cognitive capacity that allows a young adult to gain admission to medical school enough to provide lifelong protection against mental health problems? Obviously, the answer is no. As a psychiatrist, I have had several colleagues as patients over the years. They have suffered from common psychiatric disorders such as depression and anxiety, while others have had bipolar disorder or an eating disorder. They have been ordinary human beings experiencing ordinary human suffering. But what has always been different is that seeking help as a doctor is never quite the same.

Many doctors try to take care of themselves by prescribing medication for themselves, including psychiatric medication. Misuse of prescription medication is one of the most common reasons for losing one's prescribing rights in Finland. Seeking professional help may be partly inhibited by the fear of losing one's professional rights. But there are other reasons, too. In my experience, the stigma surrounding mental illness remains strong within medicine, including within psychiatry itself.

There are many jokes within psychiatry that are based on the division between healthy professionals and ill patients. Humour is, of course, one way of coping with difficult emotions. I remember laughing more than anywhere else, when I worked on an acute psychiatric ward during the first two years of my career. I have often tried to remember what it was that we laughed at. Was it madness itself? Was it, indirectly, the patients after all? One of the most common jokes is that when someone says something odd, another person asks whether their medication is "in balance". The humour relies on the implicit assumption that the professional could never be taking psychiatric medication themselves. Of course, the joke is not funny at all if the person actually is receiving psychiatric treatment that keeps them well.

I began specializing in psychiatry immediately after graduating from medical school. Psychiatry has been my passion ever since, and I have never regretted my choice. Even after 28 years, I still find working as a psychiatrist highly interesting, motivating and fulfilling. I genuinely love both the clinical work and my role as a senior consultant supporting younger colleagues. I had been somewhat of a hypochondriac ever since childhood, but I was always afraid of somatic illnesses. I was never really worried about developing a psychiatric illness myself. I was completely unprepared when, in the summer of 2004, a couple of weeks after giving birth to our third child, I experienced a mixed mood episode for the first time in my life. I had had milder mood symptoms after the births of our first two children, but this time I truly crossed the line into madness.

I did not realize that I was psychiatrically ill, although my husband tried to make me understand it. I was outraged by his suggestion. I thought he was merely trying to free himself from responsibility for my exhaustion. To be fair, I had a point. We had bought an old house before the birth and had started a complete renovation project only a couple of weeks afterwards. I had also been working and studying extensively while carrying most of the financial responsibility for supporting our family during the previous years. But my husband was right, too. I was not myself during the extreme turmoil of my mood, and I was in complete denial.

I recovered from the first mixed episode without professional care. My parents took my family into their home and looked after our children so that my husband could finish renovating our house with the help of our friends and relatives. I was completely unable to take care of our children or, almost, even of myself. My mood swung from mania to depression and irritability within minutes. I slept only a couple of hours each night and was extremely anxious. My cognitive abilities no longer functioned properly. I could not follow an ordinary conversation or read anything. On television, I could only follow the Teletubbies because every scene was repeated twice.

After a couple of weeks, I gradually understood the rhythm of my mood swings, and this reduced both the chaos and the anxiety I was experiencing. After that, I started sleeping normally again, and my mood slowly stabilized until I returned to my usual self.

We could not talk about what had happened, because my husband still believed that I had experienced a mood episode, whereas I clung to my scientifically unfounded exhaustion theory. We moved into our renovated house in August 2004 and somehow struggled through the autumn. I was tired, but my mood had become stable again. I was on maternity leave, so fortunately I had not endangered my patients' care or damaged my professional reputation. The damage had occurred within my family. It was my children and my husband who had suffered during my period of madness.

In February 2005, six months after the first episode, my mood started becoming unstable again. I thought it would pass, just as it had the first time, if only I could get some rest. But when I finally had the opportunity to rest, I realized that I was unable to calm down. This time the mood swings were even more intense, and I was extremely irritable and anxious. I realized that I needed professional help and admitted myself to a psychiatric hospital.

I was definitely not an easy patient. I believed that I knew better than anyone else what I was suffering from. My theory was that I was experiencing some kind of delirium caused by exhaustion. To me, this explanation was far more acceptable than having a genuine psychiatric disorder. My doctor offered me antipsychotic medication, but I felt deeply insulted because I had no real insight into my own condition. I refused appropriate medication during the first couple of weeks. What eventually changed my mind was a conversation with the psychologist on the ward, with whom I somehow established a better connection than I did with the doctors or nurses. She said two things that I have never forgotten. First, she asked, "Don't you see that we are worried about your ability to work?" This struck me deeply. I had not thought about it before, but I immediately realized that I would never have been able to work in the condition I was in. The second thing she said was, "You have suffered because of your profession. Any other patient would have been treated differently." As a psychiatrist, I immediately understood what she meant. She meant that any other patient would most likely have been given medication against their will. I had been able to argue my way out of treatment. That made me agree to start taking antipsychotic medication. For the first time, I truly understood how seriously ill I was.

It is somewhat remarkable that, although I had agreed to be admitted to a psychiatric hospital and to take antipsychotic medication, I still could not accept that I was actually mentally ill. I insisted on undergoing thorough diagnostic interviews and psychological assessments, which were carried out. By then I had already been discharged from the hospital and visited the psychologist as an outpatient.

When all the assessments had been completed, a meeting was held with the psychologist, the junior doctor, the senior psychiatrist of the ward, several nurses and me. These multidisciplinary meetings, which had taken place several times during my hospital stay, were extremely stressful for me. I always felt as though there was an entire group of professionals opposing me, and I found it intimidating to discuss deeply personal matters in front of so many people.

At this final meeting before the end of my hospital treatment, the senior psychiatrist told me that he would write a medical certificate so that I would be entitled to special reimbursement for my psychiatric medication from the Social Insurance Institution of Finland. I replied that I probably would not qualify because, as far as I knew, the reimbursement required a psychotic-level illness. "I will write it with the diagnosis of a mixed episode of bipolar disorder. With that diagnosis, it will be approved," he said. Those two sentences made my world come crashing down. After having completely denied my illness, I suddenly gained full insight into my situation. The realization was overwhelming and deeply painful. I had a serious mental disorder. I had been wrong, all along. My husband, the doctors and the nurses had been right.

Before becoming ill myself, I had worked as a psychiatrist for four and a half years, and all of my experience with bipolar disorder came from working on an acute psychiatric ward. I had seen only the most severe forms of the illness: psychotic mania, violent behaviour, suicidal depression, repeated hospitalization, broken families and permanent loss of the ability to work. When I received the diagnosis myself, I wondered: *Was this the future that awaited me*?

It is difficult to describe the profound sense of insecurity I experienced. It felt as though the entire foundation of my life and identity had been taken away. Would I ever be able to work again? Would I be able to take care of our children? Could I still be a good friend? Would I ever return to the life I had before? I had always trusted my ability to persevere, to work hard and to take responsibility for my duties. Alongside the fear and uncertainty, I felt overwhelming shame. When I attended my first appointments with the psychologist at the outpatient clinic to which I had been referred after discharge, I felt ashamed simply because I had become a psychiatric outpatient. After the second mixed episode subsided, I was profoundly exhausted, and my cognitive functioning remained impaired for a long time. Perhaps I was depressed as well, but more than depression it felt as though my brain had been burned out by the mixed episode. I felt as though I were recovering from a brain injury—which, in a sense, I was.

The psychologist at the hospital had once told me that sleep is nature's own medicine. I took those words seriously and slept almost around the clock. My parents worried that I had become overmedicated and emotionally blunted. Perhaps that was partly true—I was not yet accustomed to my medication—but I believe that most of the emotional flatness resulted from my psychological condition and the aftermath of the severe mixed episode I had gone through.

In many ways, I was fortunate. My husband, our parents and our friends were all unwaveringly supportive. I was completely open about my diagnosis with my family and close friends. I received both practical and emotional support, for which I will remain grateful for the rest of my life.

At the outpatient clinic I had the privilege of seeing a wise, experienced psychologist every other week. She and my husband both believed that I would recover and eventually be able to return to work. During the first year of my recovery, I cried during every single appointment with my psychologist. The crisis of having a serious mental illness completely dominated my life.

At that time, I had no way of knowing what my prognosis would be. Yet, little by little, month by month, I recovered. I was on sick leave for one year and three months. In June 2006, I returned to work as a resident in psychiatry. I was enormously relieved to discover that my professional abilities had not disappeared. I could still work.

In some ways, working as a psychiatrist became easier after my own illness. I had experienced firsthand how stressful and intimidating it is to see a psychiatrist, and how much power psychiatrists have, when assessing and diagnosing deeply personal psychological experiences. When I had been the patient, what mattered most to me was being treated as one human being by another—not being looked down upon from behind a rigid professional role.

I had also learned how important medical documentation truly is. In Finland, sickness benefits are paid and psychotherapy is reimbursed on the basis of medical certificates written by psychiatrists. Among psychiatrists, this paperwork is often considered tedious and unpopular. After my own experience as a psychiatric patient, I have never complained about it. What may seem like routine paperwork to the psychiatrist can be of enormous importance to the patient. I had learned that recovering is almost impossible if one does not know whether there will be enough money to buy food for one's children the following month.

Since returning to work 20 years ago, I have experienced only a couple of mild, short depressive episodes. Apart from those, I have remained in remission. I have been utterly committed to taking my medication every evening, and I intend to continue doing so for the rest of my life.

Once I accepted the diagnosis, I also accepted the lifestyle changes that were recommended. During the first few years, I was very strict about maintaining a regular sleep schedule. Over time, I have learned that I can tolerate quite a lot of stress. I still monitor my mood, although not nearly as obsessively as I did in the beginning. If I notice symptoms that remind me of the mixed episode—such as unusual irritability, elevated mood or inner agitation—I increase the dose of my medication and make a particular effort to get enough sleep. This strategy has enabled me to remain in remission. I do not know how much of this stability is due to taking my medication faithfully, maintaining regular routines, undergoing three years of psychotherapy, carefully monitoring my symptoms and receiving strong social support. Or whether it is partly because the particular form of bipolar I disorder that I happened to inherit has been relatively benign and responsive to treatment Most likely, it is the result of both.

I completed my specialist training in psychiatry two years after returning to work. Since then, I have now been able to work continuously. In 2022, I completed my PhD. I have served as the editor-in-chief of a psychoeducational book on bipolar disorder for patients and their families, and another book on dialectical behaviour therapy skills for people with difficulties

regulating their emotions. I have also become a member of the Finnish Current Care Guideline working group on bipolar disorder and have given numerous lectures on the illness. Alongside my medical work, I have written two collections of poetry and performed publicly as a pianist. None of these achievements have felt self-evident. Rather, they have been a source of profound gratitude and joy. I have never again taken my ability to work for granted. Instead, I regard it as a privilege.

When I was first diagnosed with bipolar disorder, I initially felt a strong urge to tell almost everyone about it. My husband advised me not to rush. "You can always tell people later," he said, "but once you've told them, you can never take the words back." I followed his advice. I was completely open about my illness with my family and close friends, but within professional circles I remained silent. There were several reasons for this.

First, I was still at the beginning of my career, and I did not want bipolar disorder to become the first thing colleagues thought of when they met me. Second, I had no idea what kind of future awaited me with this diagnosis. Third, hearing the sometimes disrespectful way in which healthcare professionals occasionally spoke about patients behind closed doors did not encourage me to be open. Would they speak about me in the same way if they knew about my diagnosis? I often asked myself that question. There was also another reason for my silence. I was afraid of how my patients might react. Would they still trust me as their psychiatrist if they knew that I had bipolar disorder?

Ever since receiving the diagnosis, I had thought that one day I would tell my story publicly. That moment came after I was diagnosed with breast cancer in January 2024. As I began writing about my experiences as a cancer patient, I realized in a very concrete way that life is finite. If I wanted to tell my story, I should do it now, before I ran out of time. This led me to write the book *Lääkärin sairauskertomus – merkintöjä syövästä, mielialahäiriöstä ja rakkaudesta* (Avain, 2025). A free English translation of the title would be *A Doctor's Case History – Notes on Cancer, Mood Disorder and Love*. I wrote the book because I wanted to contribute, in my own small way, to reducing the stigma surrounding mental illness—especially the stigma that still exists within healthcare itself. I also wanted to offer hope to people who receive a diagnosis of bipolar disorder. Finally, I wanted to describe the particular difficulties that healthcare professionals face when they themselves need psychiatric help.

I had kept my diagnosis hidden from my colleagues for twenty years. After the publication of my book, none of my fears came true. Quite the opposite. None of my previous books had generated as much spontaneous positive feedback from patients, colleagues and other readers. Meeting patients who have read my book has been an unusual experience. Traditionally, psychiatrists reveal very little about themselves to their patients. In my book, however, I share a great deal of my own life. To my surprise, this has not negatively affected my relationship with the patients who have read it. If anything, it has become easier to meet them as equals, knowing that they are aware I have gone through a serious struggle myself. The book has even brought some new patients to my private practice who specifically sought me out because they had read it.

For me, being open has been deeply integrating. I have realized that keeping a secret in itself reinforces the feeling that the secret is something shameful. Being open has proved much simpler—and much more liberating—than I had imagined.

To be fair, however, it is much easier for me to speak openly now than it would have been earlier in my career. I have worked as a psychiatrist for many years. I have been in remission for a long time. I have demonstrated my ability to work continuously for twenty years. My situation would undoubtedly be different if my mood were still unstable or if I were competing for a position that I deeply wanted.

My eldest son, who was also diagnosed with bipolar I disorder a couple of years ago, has been open about his illness from the very beginning. One day, his manager mentioned at a meeting that he had developed a stress fracture in his foot after long-distance running. My son later said to me, "Why shouldn't it be just as natural to talk about stress fractures of the mind?" I have thought about that sentence many times. To me, after finally speaking openly within professional circles, it has indeed become just that natural.

I still do not know what my future holds. It is always possible that I will experience another bipolar episode. I can never completely forget my illness. But so far, I have been able to live a rich and fulfilling life, not despite my diagnosis, but together with it. And if living through bipolar disorder has changed me in any way, I believe it has made me a more humble, more compassionate and ultimately a better psychiatrist.

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JONNA TOLONEN

OPINION: BEYOND SYMPTOM REDUCTION: THE IMPORTANCE OF PERSONAL RECOVERY IN PSYCHOTIC DISORDERS

ABSTRACT

The concept of personal recovery has gained increasing attention in mental health research and clinical practice, generating a growing body of theories and applications. However, more critical reflection is needed on how mental healthcare and wider society understand and enable personal recovery for people with psychotic disorders. This opinion paper argues for personal recovery as a central goal in the prognosis of psychosis, while drawing attention to constrained choice within mental health services and structural barriers to social inclusion, including employment and intimate relationships. Advancing recovery-oriented care requires not only supporting individual agency but also addressing the structural conditions that shape opportunities for meaningful inclusion in society.

KEYWORDS: PSYCHOSES, RECOVERY, FREEDOM OF CHOICE, SOCIAL INCLUSION

INTRODUCTION

Personal recovery has gained increasing attention in mental health services and research of severe mental illnesses, including psychotic disorders. Personal recovery is a key phenomenon of recovery orientation [1]. Recovery orientation is a framework that brings together ideas from the human rights movement, various psychological theories—such as positive psychology—and the social inclusion of people with severe mental illnesses [2]. From the point of view of mental health service users, the use of recovery orientation can improve the quality of mental health services [3,4].

Personal recovery was first defined by Anthony in 1993 as a unique, deep and individual change process of feelings, skills, values and attitudes with a central feature of personal experience of a meaningful and satisfying life despite the limitations caused by the mental illness [5]. Personal recovery is a process that is multifaceted and not straightforward, with the possibility for the person to try and fail [6]. According to a recent publication, several practical work models of personal recovery have been developed [7]. The CHIME framework is the most widely adopted model of personal recovery in both mental health practice and research [6,8]. In recent years adaptations of the CHIME [8], as well as models of personal recovery for specific diagnostic [9] and age groups [10], have been published.

The CHIME framework consists of five recovery processes: Connectedness, Hope, Identity, Meaning and Empowerment [6]. Additionally, for severe mental disorders different approaches on personal recovery have been proposed. Stuart, Tansey and Quale (2017) elaborated the CHIME framework, arguing that it should also consider Difficulties that burden persons with severe mental illness, and proposed a modification with CHIME-D [8]. Jaiswal et colleagues (2020) developed a completely new practical model of care for personal recovery: the recovery elements model. The model proposes three main elements of personal recovery: Relationships, Sense of Meaning and Participation [11]. In conclusion, existing models of personal recovery consistently highlight core elements such as social inclusion, identity, hope and a sense of meaning [7].

WHAT RESEARCH TELLS US

Fifteen years ago, Leamy and colleagues had already identified 97 scientifically developed models of personal recovery. These

models were derived primarily from qualitative research focusing on lived experiences of recovery, most often among people with psychotic disorders, including schizophrenia [6]. While firmly grounded in empirical research, this body of work reflects a predominantly qualitative tradition, and still today studying personal recovery using quantitative methods remains challenging [12,13]. As a deeply individual, non-linear process without fixed stages or a clear endpoint, personal recovery does not lend itself easily to measurement. Nevertheless, further research work is needed to establish meaningful cut-off points and reference ranges for personal recovery in different cultures.

One field of research interest has been the possible connection of personal and clinical recovery. Research has shown that they are distinctive constructs [14] with, for example, a temporal difference – personal recovery is a continuum, whereas clinical recovery is an endpoint [15]. However, also commonalities between the concepts have been found [14,16]. For instance, clinical recovery is positively associated with personal recovery, showing a relationship between the two phenomena [16,17]. Across studies, the proportion of individuals with schizophrenia who meet criteria for both clinical and personal recovery has varied widely, ranging from 5% to 38% [14,17,18].

When looking at research on personal recovery in psychotic disorders, a consistent message emerges – psychotic symptoms themselves do not define a person's capacity for recovery. Studies have repeatedly shown that symptom severity is not directly linked to personal recovery outcomes [19,20], however, affective symptoms are associated with lower levels of personal recovery [20,21]. What seems to matter in personal recovery are the subjective and relational dimensions of the phenomenon. Furthermore, in a one-year follow-up study among people with schizophrenia, Dubreucq and colleagues (2022) found that a higher level of personal recovery at baseline predicted a fivefold increase in the likelihood of clinical recovery at follow-up. At the same time, being in clinical recovery initially increased the odds of improved personal recovery threefold one year later [17]. These findings challenge symptom-focused models of care and suggest that supporting personal recovery is not a secondary goal, but a prerequisite for broader recovery outcomes. If personal recovery were seen as a first-line goal in the prognosis of psychotic disorders, what steps would need to be taken?

FREEDOM OF CHOICE UNDER CONSTRAINT

Psychiatric care has historically been marked by paternalistic practices, where decisions about care were largely made on behalf of patients rather than with them [22–24]. Within recovery-oriented practice and the concept of personal recovery, freedom of choice in one's own mental healthcare is often presented as absolute. Individuals are seen as having the right to choose whether to use mental health services—and which services to use—without these choices being judged by professionals or viewed as barriers to personal recovery [25].

In practice, however, this ideal of unrestricted choice is far from straightforward. Refusing medication, particularly in psychotic disorders, frequently places mental health service providers in a position of tension and discomfort, exposing the limits of tolerance for patient choice [26,27]. At the same time, freedom of choice is constrained by structural inequalities: evidence-based mental health interventions are not equally available across geographical regions [e.g. 27]. Moreover, organizational traditions or service provider orientations—for instance, a strong focus on trauma-informed approaches—can shape which interventions are prioritized and which remain inaccessible. As a result, what is framed as "choice" may in reality be a choice among limited or predetermined options.

On the other hand, there is a risk that an emphasis on autonomy of choice may slide into the abandonment of people who are in need of support. When "personal recovery" is treated as synonymous with complete self-management or framed through overly optimistic expectations, responsibility for recovery can be shifted almost entirely onto the individual. These risk obscuring the critical role of social context, structural conditions and access to resources in shaping recovery processes [8,29]. Autonomy and individuality are not achieved through withdrawal of support, but through relational practices—such as shared or supported decision-making—that actively recognize both personal agency and interdependence [27,30].

SOCIAL INCLUSION OR A PARALLEL SOCIETY?

From multiple perspectives, social inclusion is a key component of personal recovery. Central aspects of social inclusion are social relationships and employment [30]. Personal recovery has been closely linked to social relationships [16,31] and to quality of life [12,18,31,32], while research has shown that one important contributor of quality of life is employment [33,34], showing an indirect association between employment and personal recovery. In the literature, peer relationships

are proposed as an important means of fostering social connection among people with psychotic disorders [35,36]. These opportunities are often provided by non-governmental organizations and may even lead individuals to train as peer support workers or experts by experience.

However, I would argue that this does not necessarily promote inclusion in the wider society, but rather inclusion within a specific, marginalized subculture centred on mental health. In such contexts, one's primary reference group often consists of others with similar diagnoses. While this can be meaningful and supportive, it may not represent a form of social inclusion that suits everyone. True inclusion should also mean having the opportunity to participate in any part of society—not only in spaces defined by mental health services or identities.

One of the most persistent forms of social exclusion faced by people with psychosis is access to the open labour market. Individuals with psychotic disorders have low employment rates [37–40]. There are no simple solutions to making labour markets more inclusive, as barriers are shaped by broader structural factors such as economic conditions, changing demands of working life and employment legislation. Although various interventions have been proposed to improve employment outcomes—most notably supported employment—these approaches alone cannot address the underlying societal issues. As such, they risk focusing on adapting the individual to the labour market, rather than questioning how the labour market itself may exclude those with mental health conditions.

However, exclusion is not limited to employment; it also extends into more intimate areas of life, including close and romantic relationships. Individuals with severe mental illness value intimate relationships and perceive them as a core component of recovery [41,42]. Such relationships foster hope, connectedness and a sense of inclusion, thereby contributing to a meaningful life for people with psychotic disorders [43]. Recent research in a population with first-episode psychosis suggests that, compared to community controls, involvement in romantic relationships may be associated with greater social integration [42]. Nevertheless, mental health service providers may hold ambivalent or even negative attitudes towards these relationships [44–46]. Moreover, issues related to sexuality and intimacy are frequently marginalized or overlooked within mental healthcare settings [43,47]. This is perhaps most clearly reflected in the lack of structured interventions addressing challenges such as initiating and maintaining romantic relationships, sexuality and family formation among individuals with psychotic disorders, with only a limited number of approaches described in the literature [48,49]. In this sense, the boundaries of what is considered "appropriate" within mental healthcare may inadvertently constrain the scope of personal recovery.

CONCLUSION

The case has been made for personal recovery as the primary goal in the prognosis of psychotic disorders. To achieve this collectively, it is essential to move away from paternalistic attitudes toward psychotic disorders, both within society and in mental healthcare practices. At the same time, psychotic disorders should be recognized as illnesses rather than matters of personal choice or responsibility. Individuals living with these disorders deserve the same rights to care, rehabilitation and support as those with any other health condition. Finally, efforts should be directed toward promoting genuine social inclusion, including access to employment and meaningful social relationships. Everyone should have the opportunity to pursue a meaningful life of their own choosing.

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AI-assisted tools were used only to improve the language and readability of the manuscript. The author is solely responsible for the content and conclusions presented.

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IIRIS KÄMÄRÄINEN, LOTTA LEHMUSVUORI, ERIKA JÄÄSKELÄINEN, TUOMAS MAJURI, JONNA TOLONEN

PROPORTION OF INDIVIDUALS WITH SCHIZOPHRENIA SPECTRUM DISORDERS REPORTING PERSONAL RECOVERY AND FACTORS ASSOCIATED WITH PERSONAL RECOVERY – A SCOPING REVIEW

ABSTRACT

***Objective**: The aim of this scoping review was to collate evidence on the proportion of individuals with SSD reporting personal recovery and to identify factors associated with personal recovery.* ***Method**: This scoping review was executed in accordance with the JBI methodology for scoping reviews. Searches were conducted in Scopus and Ovid Medline in January and May of 2026. Studies were included with a study population of schizophrenia spectrum disorders (SSD), personal recovery measured with a designated measure and the proportion of participants reporting personal recovery. A quality appraisal of the included studies was performed with the JBI critical appraisal tool for Analytical Cross-Sectional studies. Results were synthesized through narrative analysis, as a weighted mean of the proportion of participants personally recovered and as a median recovery rate.* ***Results**: Seven studies, published between 2006 and 2026, met the inclusion criteria. Three different instruments to measure personal recovery were utilized in the included studies. The weighted mean proportion of individuals reporting personal recovery was 27%, ranging from 15%–83%. Six out of seven studies also analysed factors associated with personal recovery, including demographic factors, psychiatric symptoms and functioning. The quality of the studies included in the review was moderate; no study received an excellent rating and one study was rated as poor.* ***Conclusion**: Proportion of individuals with SSD experiencing personal recovery vary. Personal recovery is an important factor to consider in overall recovery and treatment of persons with SSD. More research evidence and standard thresholds are needed for personal recovery. Research on personal recovery remains limited, including in Finland, highlighting the need for further research in the Finnish context.*

KEYWORDS: SCHIZOPHRENIA, SCHIZOAFFECTIVE DISORDER, RECOVERY, ASSOCIATION, REVIEWS

INTRODUCTION

Severe mental illness (SMI) has been reported to cause a substantial human and financial burden globally (1). Schizophrenia Spectrum Disorders (SDDs) are SMIs and among the most common psychotic disorders (2,3). They affect individuals´ functioning (1), social inclusion (2), employment outcomes (3) and quality of life (4,5). Prognosis of SSDs varies individually, in relation to phase of disorder, age, and depending on which outcomes are being measured (6–8). Clinical recovery in SMIs is typically defined by symptom remission, improved functioning or a combination of these outcomes (9–11), whereas personal recovery emphasizes an individual's ability to lead a meaningful and satisfying life despite the presence of symptoms (12,13). Definitions and measures of recovery in SSD differ greatly (6) and rates of clinical recovery vary from 14% to 38% depending on the proposed criteria and time range (6,14,15).

The recovery orientation is a framework used in social and healthcare that originated from the human rights movement, combining theories of psychology and social sciences (16). As opposed to clinical recovery which focuses more on the removal of symptoms, personal recovery can be viewed as the ultimate goal of recovery orientation (17). Personal recovery is defined as a unique, individual and non-linear change process of skills, feelings, values, attitudes and with the key idea of living a satisfying life despite the limitations possibly caused by the illness (18). There is no consensus for the definition

of personal recovery, stemming from its individual nature and sensitivity to cultural differences (19). However, the CHIME framework is one of the most widely accepted for conceptualizing personal recovery and has been applied in both clinical and research settings (13,20). CHIME comprises five recovery processes: Connectedness, Hope, Identity, Meaning in life and Empowerment (21). The framework has demonstrated its utility in understanding personal recovery, with a systematic review of qualitative studies showing that approximately 70% of personal recovery narratives could be accounted for by these recovery processes (22).

Interest in the concept of personal recovery within SSD research and clinical practice has increased substantially in recent years. However, empirical evidence on the extent of personal recovery and its related determinants among individuals with SSD remains scarce. Differences in how personal recovery is conceptualized and measured, together with considerable heterogeneity across study populations and settings, make it difficult to draw firm conclusions regarding the proportion of persons reporting personal recovery and associated factors (20). In contrast, clinical remission and recovery are widely studied in SSD research (10,23). Multiple self-report questionnaires have been developed to assess personal recovery. A recent review identified a total of 25 such instruments (24). Commonly used measures include the Recovery Assessment Scale (RAS) (25), the Questionnaire about the Process of Recovery (QPR) (26,27), the Stages of Recovery Instrument (STORI) (28) and the Mental Health Recovery Measure (MHRM) (29). Despite personal recovery being important for the individuals diagnosed with SSD and their significant others, and the increased interest on the topic (30,31), particularly in Finland research on personal recovery remains limited.

Given the conceptual diversity of personal recovery, the variety of measurement instruments and the heterogeneity of the available evidence, a scoping review was considered the most appropriate approach for mapping the existing literature. Scoping reviews are particularly suitable for topics characterized by conceptual diversity, methodological variability and heterogeneous evidence that cannot be adequately addressed through more narrowly defined systematic reviews. Such reviews enable the mapping of existing research, identification of knowledge gaps and formulation of directions for future studies (32).

The aim of this study was to estimate the proportion of individuals with SSD reporting personal recovery and examine factors associated with personal recovery. The research questions were the following:

a. What is the proportion of individuals with SSD reporting personal recovery and what instruments are used to measure personal recovery?
b. What factors have been examined in relation to personal recovery, and what associations have been reported in the literature included in the review?

The results of this scoping review can support clinical practice, future research and the development of interventions promoting personal recovery.

METHODS

The scoping review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews (32) and reported following the PRISMA guidelines for Scoping Reviews (33).

SEARCH STRATEGY

Searches were made from two electronic databases, Scopus and Ovid Medline, using relevant search and MESH terms described in detail in *Table 1*. Scopus and Ovid Medline were chosen due to covering multiple disciplines (e.g. medicine, health sciences, psychology, social sciences). We conducted an initial search on January 15, 2026 and a supplementary search on May 11, 2026. Initial search was done as part of the Bachelor of Medicine thesis (done during the first year of medical studies in University of Oulu). A second, supplementary search was conducted with slightly broader search terms to ensure the identification of all relevant studies. Electronic search was accompanied by a non-systematic manual search from the full texts of the studies included in the scoping review. Manual searching did not include systematically checking all reference lists nor citation tracking. Grey literature was not included.

Table 1. Search strategy and search terms for a scoping review on personal recovery in schizophrenia

Database	Search terms	Number of references
Initial search Jan 15, 2026		
Scopus	(TITLE-ABS-KEY ((person* OR "patient-based" OR "consumer-based" OR subjective*) W/2 (recovery OR rehabilitation OR remission)) AND TITLE-ABS-KEY (schizo*) AND TITLE-ABS-KEY ((prevalence OR incidence OR epidemiology OR occurrence OR frequency OR rate) OR (predictor* OR correlate* OR "influencing factor*" OR "associat* factor*" OR contributor*)) AND NOT TITLE-ABS-KEY ("meta-analysis" OR "review")) AND (LIMIT-TO (LANGUAGE , "English"))	141
Ovid Medline	(TITLE-ABS-KEY ("serious mental ((((person or "patient-based" or "consumer-based" or subjective).ab,kf,ti. adj3 (exp Rehabilitation/ or exp Psychiatric Rehabilitation/ or (recovery or rehabilitation or remission).ab,kf,ti.)) and ((exp Schizophrenia, Disorganized/ or exp Schizophrenia, Treatment-Resistant/ or exp "Schizophrenia Spectrum and Other Psychotic Disorders"/ or exp Schizophrenia, Paranoid/ or exp Schizophrenia, Catatonic/ or exp Schizophrenia, Childhood/ or exp Schizophrenia/) or ("schizo".ab,kf,ti.)) and (exp Prevalence/ or exp Incidence/ or exp Epidemiology/ or ((prevalence or incidence or epidemiology or occurrence or frequency or rate).ab,kf,ti.) or ((predictor or correlate or "influencing factor" or "associat factor" or contributor*).ab,kf,ti.))) and english.lg) not ((review or meta-analysis).pt. or (review or meta-analysis).ti.)	266
Supplementary search May 11, 2026		
Scopus	(TITLE-ABS-KEY ((perso* OR subjective OR psychological) W/2 recovery) AND TITLE-ABS-KEY (schizo*)) AND (LIMIT-TO (LANGUAGE , "English")) AND (EXCLUDE (DOCTYPE , "re"))	460
Ovid Medline	(((person OR psychological OR subjective) ADJ3 recovery) AND schizo*) NOT (review.pt. OR meta-analysis.pt.) AND english.lg) producing a total of 104 references.	104
		Total 833

Abbreviations: CI=Confidence Interval, HR=Hazard Ratio

INCLUSION AND EXCLUSION CRITERIA

For inclusion in this scoping review, studies were required to meet the following criteria: a) primary empirical articles written in English, b) reporting the proportion of participants reporting personal recovery, c) ≥80% of the study participants having a diagnosis of SSD (schizophrenia spectrum disorder including schizophrenia, schizoaffective disorder and schizophreniform disorder), d) personal recovery being measured with an instrument specifically designed for this purpose (24).

The exclusion criteria were as follows: a) articles that were not primary empirical studies (for example, review articles, commentaries or letters to the editor), b) qualitative or case studies, c) articles written in any other language than English, d) studies reporting personal recovery only as a mean or median of the sample (not reporting proportion of individuals reporting personal recovery), e) >20% of the participants with a diagnosis other than SSD, f) personal recovery measured using other instruments not specifically designed for assessing personal recovery, e.g. a quality of life measure.

STUDY SELECTION

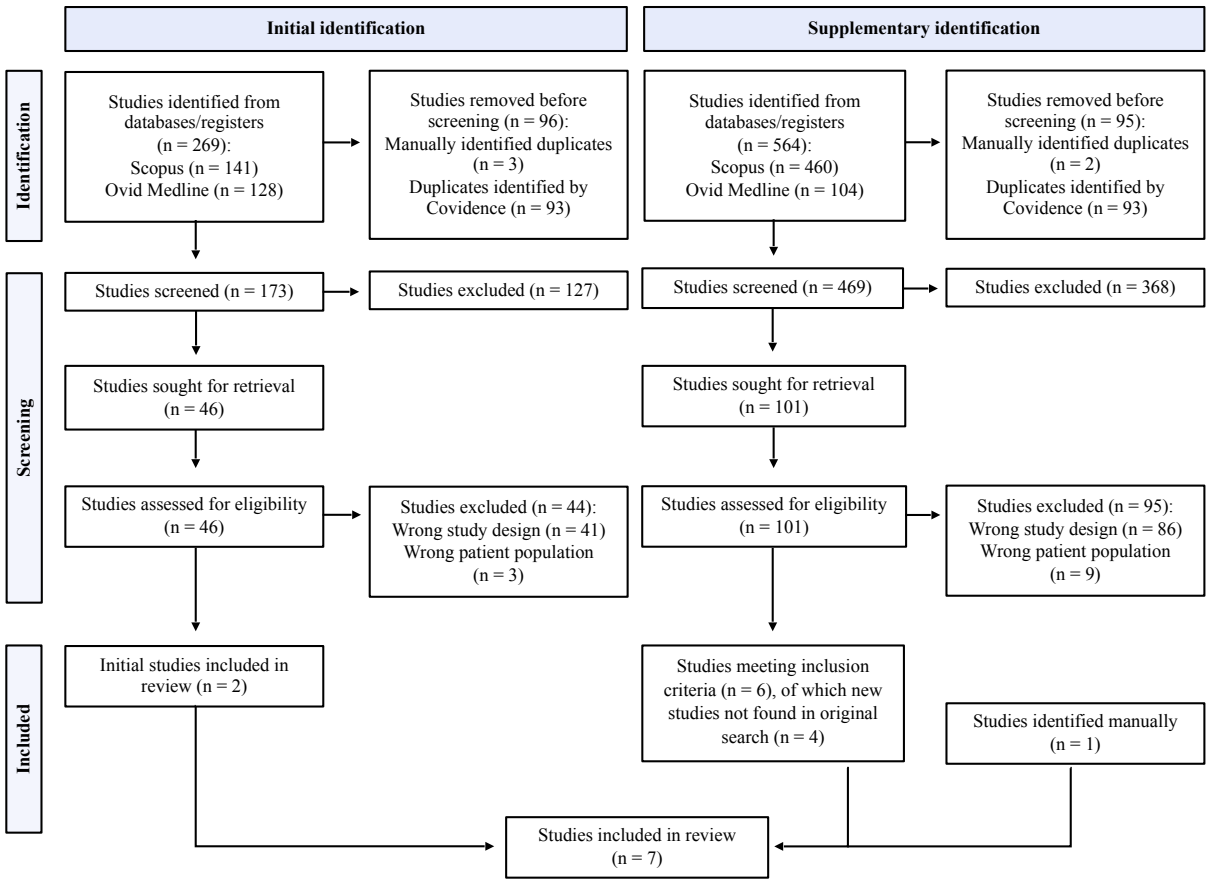
In the first search, two independent reviewers (IK, LL) conducted the title/abstract screening and full-text screening against the eligibility criteria in Covidence. Covidence is a web-based collaboration software platform that streamlines the production of systematic and other literature reviews (34). Disagreements were resolved by a third reviewer (EJ).

A supplementary search was subsequently conducted using broader search terms. The broader search strategy resulted in a substantially larger number of records being identified, compared with the initial search. This difference reflects the wider range of search terms applied in the supplementary search rather than any changes to the review objectives or eligibility criteria. Records identified in the supplementary search were compared

with those from the initial search using DOI identifiers, and duplicates were removed. Given that the supplementary search was primarily intended to identify additional studies not captured in the initial search, the screening process was conducted by a single reviewer (JT or EJ). Eligibility decisions were discussed among the reviewers whenever uncertainty arose. The workload was divided between reviewers (JT, ET), with each reviewer screening approximately 50% of the records at both the title and abstract and the full-text review stages.

Finally, a non-systematic manual search was conducted from the full texts of the included studies. Any additional studies identified were assessed for eligibility through full-text screening. The search and study selection process is presented in PRISMA flow diagram in *Figure 1*.

Figure 1. PRISMA flow diagram. The search and study selection process



DATA EXTRACTION AND SYNTHESIS

Data extraction was conducted collaboratively by three reviewers (IK, LL, JT) using a structured form. Extracted data included: a) authors, b) year of publication, c) country of origin, d) data collection period, e) sample size and diagnosis of participants, f) the instrument and threshold used to assess personal recovery, g) proportion of participants who achieved personal recovery, h) associated factors and i) comments. Data on the study setting and average duration of illness were extracted if reported.

The results are presented through a weighted mean recovery rate, median recovery rate and narrative synthesis of factors associated with personal recovery, and tables that correspond to the objectives of this scoping review. These methods were selected in accordance with JBI guidance for scoping reviews (32). The weighted mean recovery rate was calculated to account for differences in study sample sizes by dividing the total number of recovered individuals in all studies by the total sample size across studies, while the median recovery rate was determined from the distribution of study-level percentages as the central value. One study was rated as low quality in the quality assessment and was therefore excluded in a sensitivity analysis for the weighted mean recovery rate, to evaluate its potential influence on the weighted recovery estimate.

QUALITY ASSESSMENT OF THE STUDIES

The quality assessment of the studies was done with the JBI critical appraisal tool for Analytical Cross-Sectional studies which includes eight items rated ´yes`, ´no` and ´not applicable` (35).The assessment was done in pairs of researchers so that each pair assessed approximately 50% of the studies (IK & EJ 4 studies; LL & JT 3 studies), results and disagreements were discussed and settled by pairs (IK & EJ; LL & JT), and all together if needed. The quality of the study did not affect inclusion in this review.

ETHICAL APPROVAL

Ethical approval was not required because the study was a scoping review based on existing published data. This study was done in accordance with Declaration of Helsinki (36) and Finnish guidance on responsible research (37).

RESULTS

SEARCH RESULTS AND STUDY SELECTION

The search and selection process is illustrated in *Figure 1*. The initial search yielded 269 studies and the supplemental search 564 studies (in total 833, *Table 1*) and 642 studies were retained after duplicates were removed. The larger number of records identified in the supplementary search was attributable to the broader search terms used. In the supplemental search, retained studies were compared to the initial search results and 100 duplicate studies were removed. After title and abstract screening, 147 studies were assessed for eligibility. 139 studies were excluded, and the reasons for exclusion were wrong study design and wrong patient population. Six studies met the eligibility criteria and were included in the review. Finally, we conducted a manual search from the studies included in the review for possible new eligible studies to be included in the scoping review, and found one new study to be included in the review. A total of seven studies were included in the scoping review.

DESCRIPTION OF THE INCLUDED STUDIES

The two searches yielded seven studies, and their study characteristics are presented in *Table 2*. Studies were published between 2006-2026. There was one Randomized Controlled Trial (RCT) (38), one cohort study (39) and five cross-sectional studies (28,40–43). Two studies were conducted in France (39,40), two in China (38,43), one in Spain (42), one in Australia (28) and one in United Kingdom (41). The sample sizes varied between 94 and 1239 participants. Two studies reported the average duration of illness, which was 10.23 years (39) and 18.23 years (28). Five studies (38–40,42,43) reported that the participants were receiving outpatient care and two studies reported that some of the participants were receiving outpatient care and some inpatient care (28,41).

Table 2. Summary of studies (n=7) included in the scoping review

Authors, Year, Country	Study design and purpose	Study characteristics	Instrument used to assess personal recovery; threshold	Proportion of personally recovered participants n (%)	Factors associated with personal recovery 0 = no association + = positive association – = negative association	Comments
Andresen et al. (2006), Australia (28)	Cross-sectional study; the aim of the study was to examine the validity of the STORI, first, as a measure of the recovery construct and second, as a measure of the stages of recovery	The data collection period was not reported; n=94 (schizophrenia diagnosis); the average duration of illness 18.23 years; outpatient and inpatient sample	STORI; participants who were classified in stage 4 (rebuilding) or stage 5 (growth) met the criteria for personal recovery	78 (83.0%)	Age 0 Age at onset 0 Gender 0 Country of birth 0 Duration since diagnosis 0 More time since last inpatient treatment + Length of last inpatient treatment 0 Higher education level +	–
Best et al. (2020), United Kingdom (41)	Cross-sectional study; the aim of the study was to examine differential predictors of personal and functional recovery in psychosis	Data collection 2007–2016; n=857 (schizophrenia or other psychotic disorder); outpatient and inpatient sample	QPR-15; participants who scored at least 45 points met the criteria for personal recovery	124 (14.5%)	Age 0 Gender 0 Positive symptoms 0 Lower level of negative symptoms + Lower level of depressive symptoms + Higher level of disorganized symptoms + Higher level of excitement symptoms + Lower level of emotional distress of hallucinations and delusions + Cognitive interpretation of hallucinations and delusions 0 Physical symptom characteristics hallucinations 0 Better functioning +	The data in this study was combined from four different studies (three cognitive behavioural therapy trials, one study on the process of recovery). Majority of participants were treatment-seeking. Inclusion criteria for the clinical trials included active psychotic symptomatology. In this case most of the sample would not qualify for symptomatic recovery which might influence the results of personal recovery

Authors, Year, Country	Study design and purpose	Study characteristics	Instrument used to assess personal recovery; threshold	Proportion of personally recovered participants n (%)	Factors associated with personal recovery 0 = no association + = positive association – = negative association	Comments
Chu et al. (2026), China (38)	A 12-year follow-up of RCT on early intervention; the aim was to systematically examine rates and predictors of symptomatic remission, functional recovery, personal recovery, clinical recovery and full recovery at 12-year follow-up	The data collection period was not reported; n=103 (SSD diagnosis); outpatient sample	QPR-15; participants who scored at least 45 points at 12-year follow-up met the criteria for personal recovery	52 (50.5%)	Age 0 Age of onset 0 Gender 0 Duration of untreated psychosis 0 Medication adherence 0 Use of second-generation antipsychotics 0 Inpatient treatments 0 Lower level of premorbid schizoid and schizotypal traits + Premorbid adjustment 0 Insight 0 Lower level of positive symptoms at baseline + Positive symptoms at follow-up 0 Negative symptoms at baseline 0 Lower level of negative symptoms at follow-up + Lower level of depressive symptoms at baseline + Depressive symptoms at follow-up 0 Disorganization symptoms at baseline 0 Lower level of disorganized symptoms at follow-up + Lower level of excitement symptoms at baseline + Excitement symptoms at follow-up 0 Better psychosocial functioning + Education level 0 Employment +	All the participants were registered in the EASY programme, which only treated individuals aged 15-25 years. Therefore, these findings may not be generalizable to older patient populations. In addition, the attrition bias (a total of 54 participants were lost to follow-up at the 12-year assessment) may contribute to an overestimation of remission and recovery rates
Dubreucq et al. (2021), France (40)	Cross-sectional study; the aim of the study was to investigate sex differences in objective and subjective aspects of recovery and psychiatric rehabilitation needs in a multicentre psychiatric rehabilitation SSD sample	Data collection 1/2016 – 11/2019; n=519 (SSD diagnosis); outpatient sample	STORI; participants who were classified in stage 4 (rebuilding) or stage 5 (growth) met the criteria for personal recovery	304 (58.6%)	Gender 0	The participants were mostly men (74.4%)

Authors, Year, Country	Study design and purpose	Study characteristics	Instrument used to assess personal recovery; threshold	Proportion of personally recovered participants n (%)	Factors associated with personal recovery 0 = no association + = positive association – = negative association	Comments
Dubreucq et al. (2022), France (41)	Cohort study with a 1-year follow-up; the aim of the study was to examine the overlap and mutual distinctions between clinical and personal recovery	Data collection 2010 – 2019; n=1239 (SSD diagnosis); average duration of illness 10.23 years; outpatient sample	STORI; participants who were classified in stage 4 (rebuilding) or stage 5 (growth) met the criteria for personal recovery	217 (53.8%)	Gender 0 Age at onset 0 Lower level of depressive symptoms + Insight 0 Cognition 0 Better quality of life + Better clinical recovery +	A high proportion of participants (59.1%) were lost to follow-up. However, the participants present at follow-up did not differ at baseline from those lost to follow-up
Lemoz-Giráldez et al. (2015), Spain (42)	Cross-sectional study; the main aim of the study was to examine the psychometric properties of the STORI	Data collection 2011-2012; n=95 (schizophrenia diagnosis or schizoaffective disorder); outpatient sample	STORI; participants who were classified in stage 4 (rebuilding) or stage 5 (growth) met the criteria for personal recovery	58 (61%)	NA	The small sample size was a limitation in this study, especially the small proportion of women (29.5 %)
Yu, Zhou, et al. (2022), China (43)	Cross-sectional study; the aims of the study were to investigate the overlap between clinical and personal recovery and identify correlates of each	Data collection 5/2019 – 9/2019; n=356 (schizophrenia diagnosis); outpatient care	RAS-8; participants who scored at least 32 points met the criteria for personal recovery	62 (17.4%)	Younger age + Younger age at onset + Delayed diagnosis 0 Medication adherence 0 Higher level of psychiatric symptoms – Relationship status 0 Better functioning + Higher educational level + Employment + Lower levels of dangerous behaviour + Better quality of life + Better clinical recovery +	Participants included only those who were registered in the 686 Programme and visited the health centre during the study period. In addition, all the participants were living with their family members in one city in China (Changsha)

Abbreviations: SDD=Schizophrenia Spectrum Disorders, STORI=Stage of Recovery Instrument, RAS-8=8-item short-form version of the Recovery Assessment Scale, QPR–15=The Questionnaire about the Process of Recovery

PERSONAL RECOVERY MEASURES

In the seven included studies, three different measures of personal recovery were identified: the Stage of Recovery Instrument (STORI), the 15-item Questionnaire about the Process of Recovery (QPR-15) and the 8-item short form of the Recovery Assessment Scale (RAS-8). The thresholds and operational definitions of personal recovery varied across these instruments. Personal recovery was defined as stage 4 (rebuilding) or stage 5 (growth) on the STORI (39,40), as a score of ≥45 in the QPR-15 (38) and as a score of ≥32 on the RAS-8 (43). For studies that did not specify a threshold for personal recovery and used the STORI instrument (28,42), the STORI cut-off values proposed by Dubreucq and colleagues (2021) (40) and Dubreucq and associates (39) were applied.

THE RATE OF PERSONAL RECOVERY FROM SSD

In the included studies, the proportion of individuals reporting personal recovery ranged from 14.5% to 83.0% (*Table 2*). The weighted mean recovery rate was calculated across the study populations, which was 27.4%, with the median recovery rate being 50.5%. We conducted a sensitivity analysis for the weighted mean recovery rate, excluding the study of Andresen and colleagues (2006) (28) with a low study quality (*Table 3*). After this amendment the recovery rate was 25.78%.

FACTORS ASSOCIATED WITH PERSONAL RECOVERY

Six of the seven studies included in the scoping review reported factors associated with personal recovery (28,38–41,43). The individual factors and associations varied between studies.

Considering participant characteristics, one study reported that younger age and earlier age at onset were positively associated with personal recovery (43). In contrast, three studies found no association between age (28,38,41), or age at onset of SSD (28,38,39), and personal recovery. Regarding gender, six studies found no association with personal recovery (28,38–41,43).

Greater levels of psychiatric (43), negative (38,41) and depressive symptoms (38,39,41) were negatively associated with personal recovery. Concerning disorganized and excitement symptoms there was contradictory evidence, with studies reporting both negative (38) and positive associations in relation to personal recovery (41). Chu and colleagues (2026) also reported a negative association between baseline positive symptoms and personal recovery (38), whereas another study found no significant association between positive symptoms and personal recovery (41).

Functioning (43) and psychosocial functioning had a positive association with personal recovery (38), as did having

Table 3. Quality appraisal of the studies included in the scoping review based on JBI Critical appraisal Checklist for Analytical Cross-Sectional Studies (29)

Study	Inclusion and exclusion criteria clearly defined	Study subjects and setting described in detail	Reliable and valid exposure measurement	Objective standard criteria for condition measurement	Confounding factors identified	Strategies to deal with confounding factors stated	Reliable and valid outcome measurement	Appropriate statistical analysis used
Andresen et al. 2006	No	No	No	No	No	No	Yes	No
Best et al. 2020	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Chu et al. 2026	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Dubreucq et al. 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dubreucq et al. 2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Lemos-Giráldez 2015	Yes	Yes	N/A	Yes	No	No	Yes	Yes
Yu et al. 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes

Yes
No
N/A = Not applicable

higher education (28,43) and being employed (43). In a 12-year follow-up study of early intervention services, baseline employment was also associated with better personal recovery at follow-up (38). One study found no association between cognitive functioning and personal recovery (39), and two studies reported that insight was not associated with personal recovery (38,39).

Two studies demonstrated associations between clinical recovery and personal recovery (43,44). In a one-year follow-up study, baseline clinical recovery predicted a threefold greater likelihood of personal recovery at follow-up (44). In a cross-sectional study, the correlation between personal and clinical recovery was small (43). Moreover, two studies included in the review examined quality of life as a factor associated with personal recovery and found a positive association between the two constructs (39,43).

RESULTS OF THE QUALITY APPRAISAL

The results of the quality appraisal of the included studies are presented in *Table 3*. The majority of studies (6/7) were rated as being of moderate quality, having received six or more ´yes` or ´not applicable` ratings out of eight items (38–43). None of the studies included in this review achieved an excellent quality rating. One study was rated as poor quality, receiving only one "yes" rating out of eight (28). Several methodological limitations were identified across the included studies. A key limitation was the inadequate identification and management of confounding variables. Notably, two of the eight items in the quality appraisal tool addressed confounding, which had a substantial impact on the overall quality ratings of the studies. Also, two studies demonstrated weaknesses in the reliable and valid measurement of exposures, as defined in the JBI quality appraisal tool (35).

DISCUSSION

The aim of this study was to estimate the proportion of individuals reporting personal recovery and to explore the factors associated with personal recovery in SSD. Only seven studies met the inclusion criteria. The principal finding of the study was that the mean weighted proportion of individuals reporting personal recovery within the study populations was 27%, with a large range of diversion in mean proportions. Most of the studies also reported factors associated with personal recovery, including participant characteristics, psychiatric symptoms and functioning.

A substantial variation in recovery rates was observed (15%–83%) and the distribution of recovery rates was skewed. Smaller studies tended to report markedly higher recovery proportions, whereas larger studies consistently demonstrated lower rates. This discrepancy may indicate potential small-study effects or differences in study populations and methodology. Additionally, the measure of personal recovery may have influenced results, as personal recovery measured with the STORI instrument (28,39,40,42) produced higher recovery rates compared to QPR (38,41) and RAS (43). Following the sensitivity analysis, in which one low-quality study was excluded, the estimated recovery rate decreased from 27% to 26%. This modest change suggests that study quality may have some influence on the results, although its overall impact appears limited.

FACTORS ASSOCIATED WITH PERSONAL RECOVERY - COMPARISON TO PREVIOUS LITERATURE

Evidence is mixed concerning the factors associated with personal recovery among individuals with SSD. In this review, the association of age on personal recovery showed mixed results (28,38,41,43) and gender had no association with personal recovery (28,38–41,43). In previous research, the association of age on personal recovery has shown inconsistent results, with other studies finding younger age (31), and others older age, having an association with personal recovery (45). Regarding the role of gender in personal recovery, previous studies have identified a positive correlation between male gender and improved personal recovery outcomes (46,47). The inconsistent findings may partly reflect methodological differences between studies, for instance, including differences in the operationalization of age and the age or gender distributions of the study samples. They may also suggest that demographic characteristics such as age or gender have a relatively limited influence on personal recovery, which is likely to be shaped more strongly by psychological, social and environmental factors. It has also been proposed that the current treatment of SSD might not target personal recovery efficiently (31).

Previous research has consistently indicated that positive symptoms of psychotic disorders are not associated with personal recovery (48–50), which is also consistent with the findings of the present review; only one of the included studies reported a significant association at baseline (38). In contrast, this review reinforces earlier evidence demonstrating an association between depressive and negative symptoms and personal recovery (38,39,41), as also reported in previous literature (30,50,51).

Several explanations may account for these findings. One plausible interpretation is that affective symptoms have a more pronounced impact on an individual's capacity to experience hope, engage in social relationships and maintain everyday functioning than positive psychotic symptoms. Hope, social connectedness and a sense of meaning in life are central components of personal recovery (19) and are therefore likely to be more directly influenced by depressive symptomatology. This interpretation is further supported by evidence demonstrating a positive association between personal recovery and functional outcomes, also shown in this review (38,43).

Associations between quality of life and personal recovery have been widely reported (31,45,52). However, despite their correlation, these constructs appear to have partially distinct determinants (52) and reflect different dimensions (45). One study included in this review, Yu, Zhou, et al. (2022), identified quality of life as the only factor associated with both clinical and personal recovery (43). There is also some evidence suggesting that improvements in both personal recovery and quality of life may be less pronounced than improvements in clinical (symptomatic) recovery (8,31). Since personal recovery does not improve to the same extent as clinical recovery, interventions specifically targeting personal recovery would be needed.

Even though a substantial body of evidence exists on factors associated with personal recovery in SSD, the findings are often contradictory (28,31,38–41,43). Future research would benefit from a systematic review focusing specifically on these associated factors. Such a review should assess not only the direction but also the strength of associations through effect size estimates, and should consider methodological quality of the included studies when interpreting and weighting the results. This would enhance our understanding of personal recovery and support the development of mental health services and interventions aimed at promoting personal recovery. In addition, future research should more carefully consider the influence of cultural factors on personal recovery and its associated determinants.

CLINICAL IMPLICATIONS

A substantial proportion of studies were excluded during the screening process because personal recovery was operationalized as a continuous construct, typically reported as a mean score of personal recovery scale, and not presenting the proportion of individuals experiencing personal recovery (46,53). This is understandable given the inherently individual and dynamic nature of personal recovery, which is often conceptualized as a subjective and evolving process. Such approaches are valuable, as they enable the identification of factors associated with personal recovery and provide insight into how recovery develops and fluctuates over time among individuals with SSD. However, when measured solely as a continuous variable, these findings may be challenging to translate into clinical practice, for example in psychoeducation or service planning, as well as into population-level research. Therefore, there is also a need to categorize personal recovery in a meaningful way, while at the same time acknowledging the importance of qualitative approaches in capturing its complexity.

Notably, despite the growing body of research evidence, personal recovery remains under-represented in clinical guidelines. For instance, neither Finnish Current Care guidelines for schizophrenia treatment (54) nor recent international guidelines (55) explicitly address personal recovery outcomes. This highlights an important gap between research and clinical practice, and underscores the need to more fully integrate personal recovery into treatment frameworks. Ideally treatment for SSD should be tailored to the individual by developing a shared care plan together with the person and their family members, using shared or supported decision-making approaches (56,57). Emerging evidence also suggests that certain interventions, such as peer-support interventions (58,59) and recovery colleges can improve personal recovery among individuals with mental illness (60). In this context, it is important to consider personal recovery as a meaningful goal that healthcare service providers can actively support, as well as an important outcome to be considered in intervention research.

In a qualitative follow-up study of individuals with first-episode psychosis, which was not included in the present review, participants emphasized the importance of the temporal dimension of personal recovery, particularly in terms of accepting change across the life course. For example, participants recognized that it is not possible to maintain control over all aspects of life, and that personal agency plays a central role in the recovery process. In contrast, clinical recovery may be perceived as a more standardized, "one-size-fits-all" approach, in which recovery is defined by the mental health services and service providers rather than by individuals with SMI themselves (61). Therefore, in light of both the findings of this review and previous literature, efforts to promote personal recovery in clinical practice are essential, particularly as identifying factors that support personal recovery may inform the development of targeted interventions. For instance, the evidence suggests focusing on affective symptoms of SSD may be more beneficial for personal recovery, for instance, via interventions targeting emotional regulation (30,38,39,41,50,62). It is also noteworthy

that promoting personal recovery may, in turn, facilitate clinical recovery (43,44). Furthermore, a more precise understanding of personal recovery and its associated factors enables more effective communication with individuals with SSD, their significant others and mental health service providers.

CONSIDERATIONS ON THE QUALITY OF THE STUDIES

The overall methodological quality of the included studies was moderate, with none achieving an excellent rating. Several common limitations were identified, particularly related to the inadequate identification and management of confounding variables, which substantially influenced overall quality ratings. Only one study appropriately addressed confounding, while others either failed to identify relevant confounders or applied incomplete strategies to control for them. Two studies demonstrated weaknesses in the reliable and valid measurement of exposures. However, in certain cases, this limitation may reflect broader issues related to measurement consistency. Dubreucq et al. (2022) reported that data were collected across multiple treatment sites without employing procedures to ensure inter-site reliability (39). This limitation may affect the consistency of measurements overall and may be particularly relevant for outcome assessment. Notably, more recent studies (38,39) generally received higher quality ratings compared to older studies (28).

Recovery in schizophrenia has been studied for several decades, yet its conceptualization remains methodologically challenging. In particular, clinical, functional, social and complete recovery have been defined in numerous ways, with no universally accepted operational definition (7,49,63,64). Personal recovery is a more recent concept that emphasizes an individual's subjective experience of living a meaningful and satisfying life despite the limitations imposed by mental illness (18,21). However, personal recovery also lacks a single, universally accepted definition (19,20) and a gold standard measurement instrument (24). Furthermore, cultural factors may influence how personal recovery is experienced and interpreted (65). Existing studies have applied different conceptual frameworks and a variety of assessment tools to measure personal recovery, contributing to substantial methodological heterogeneity across the literature. This variability complicates comparisons between studies, limits the synthesis of findings, and may partly explain inconsistencies in the reported associations between potential determinants and personal recovery. These methodological considerations should therefore be taken into account when interpreting the findings of the present review. Future research should prioritize rigorous methodological approaches, including the clear identification and control of confounding variables and the use of reliable and standardized measurement procedures.

STRENGTHS AND LIMITATIONS

A major strength of this study is its focus on the proportion of persons reporting personal recovery in SSD, for which the existing evidence base remains limited and no previous review has been conducted. This scoping review followed systematic and predefined methods, adhering to the JBI methodology for scoping reviews (32), the JBI critical appraisal tool for Analytical Cross-Sectional studies was used for quality assessment (35) and reporting in accordance with the PRISMA Extension for Scoping Reviews guidelines (33). However, knowledge user consultation was not included in this review, although it is recommended in scoping review methodology (66). Such consultation could have enhanced the relevance and applicability of the findings by incorporating perspectives from stakeholders, such as service users and clinicians, by supporting the translation of results into practice.

Several limitations should also be considered. In the initial search the title and abstract screening was conducted by two independent reviewers and disagreements were resolved by a third reviewer. However, in the supplementary search reviewers split the screening of the search results and discussed obscurities, as this search was primarily intended for identifying new studies. Nevertheless, this can be seen as a limitation. Quality appraisal of the included studies was conducted by two independent reviewers, and consensus discussions were held. These factors reduced the risk of assessment errors and increased the reliability of our study findings.

A major limitation of this review is that the literature search was restricted to two electronic databases. Although these databases provide extensive coverage of the relevant literature, searching additional databases might have identified further eligible studies and increased the comprehensiveness of the review. Furthermore, grey literature was not included in this review, even though it might have provided additional relevant data on personal recovery. However, due to resource limitations, this review was limited to peer-reviewed studies in accordance with its objectives. Further limitations include the fact that the reference lists of the included studies were not searched nor forward citation tracking performed. In addition, the exclusion of qualitative studies, which could have provided a broader understanding of personal recovery, represents a limitation; however, expanding the study objectives further would have reduced feasibility.

A further limitation is that some studies reported personal recovery only as a sample mean or median rather than as the proportion of individuals reporting personal recovery. As noted previously, several self-report instruments are used to assess personal recovery, and these measures differ to some extent in their content, reliability, validity and the results they produce (24) . Consequently, the inclusion of findings based on different personal recovery measures may have affected the comparability of the results and introduced some uncertainty into the findings of this review. Nevertheless, given the limited evidence available on personal recovery among persons with SSD, we considered it important to include all eligible studies. In addition, the charting form used to summarize the extracted data was not piloted or calibrated prior to data extraction. Finally, although factors associated with personal recovery were identified and summarized, the strength of these associations was not reported in this review.

CONCLUSION

In conclusion, while personal recovery has been extensively studied in the context of severe mental disorders, research focusing specifically on personal recovery among individuals with SSD is still called for. To date, no studies have been conducted in Finland. Furthermore, the context of personal recovery in SSD has been studied only to a limited extent, and the findings of the existing studies vary considerably. The proportion of individuals reporting personal recovery in SSD was found to be approximately one quarter, most studies also reported on associations between different factors and personal recovery. This considerable variability is likely due to the small number of included articles and therefore the small amount of available data, as well as the individual limitations of the studies, which may have biased the findings. In addition, the study samples differ greatly from one another. To achieve more consistent and comparable results in the future, it would be necessary to create meaningful reference values of personal recovery. Further research is needed on individuals reporting personal recovery in SSD and the factors influencing this, in order to obtain more reliable and generalizable knowledge. Such information would provide a stronger basis for developing treatment practices and could thereby promote personal recovery for persons with SSD.

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CRediT authorship contribution statement

Iiris Kämäräinen: Investigation, Validation, Formal Analysis, Writing – Original draft and review & editing, Visualization. Lotta Lehmusvuori: Investigation, Validation, Formal Analysis, Writing – Original draft and review & editing. Tuomas Majuri: Writing – Original draft and review & editing, Visualization. Erika Jääskeläinen: Conceptualization, Writing – Review & editing, Supervision. Jonna Tolonen: Conceptualization, Methodology, Formal Analysis, Investigation, Validation, Writing – Original draft and review & editing, Visualization, Supervision.

Disclosure of AI Use

The authors used an AI-based language model to support the research process. The tool was utilized for language editing, clarification of methodological concepts, assistance with data handling (e.g. Excel-based comparisons and calculations) and literature identification. All outputs were critically reviewed and verified by the authors, who take full responsibility for the content of the manuscript.

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THE CLOZAPINE LEGACY: FUTURE DIRECTIONS IN TREATMENT-RESISTANT SCHIZOPHRENIA AND PARKINSON'S DISEASE PSYCHOSIS

ABSTRACT

Clozapine is an exceptionally potent atypical antipsychotic medication that was developed in the 1950s and is notable for a low affinity for the dopamine D2 receptor. Following multiple fatal cases of agranulocytosis, the drug was withdrawn from the market but later reinstated with strict laboratory monitoring. Despite the risks, clozapine is regarded as the most effective medication in two different types of psychosis: treatment-resistant schizophrenia and psychosis in Parkinson's disease. Although the landmark studies demonstrating the effectiveness of clozapine in both conditions were published decades ago, it remains strikingly underutilized, possibly due to risk of serious adverse effects, clinician reluctance and lack of experience and administrative complexity. It is unlikely that clozapine will ever fully escape these barriers, and continued delays in initiating effective treatment will therefore continue to undermine care. Gladly, novel treatment alternatives are emerging for both disorders. Over the past two decades, focus has shifted from dopaminergic strategies towards pharmacological agents targeting other neurotransmitter receptors that have a role in psychosis. In particular, pimavanserin, a serotonin receptor antagonist/inverse agonist, has been approved for psychosis in Parkinson's disease, and glutamate modulating compounds have been shown to enhance the effectiveness of clozapine in treatment-resistant schizophrenia. Moreover, agonists of acetylcholine receptors may hold theoretical promise for improving outcomes across both conditions. This narrative review explores the future direction that treatment of both disorders may take.

KEYWORDS: CLOZAPINE, PARKINSON'S DISEASE PSYCHOSIS, TREATMENT-RESISTANT SCHIZOPHRENIA, SCHIZOPHRENIA

PATHOGENESIS OF POSITIVE SYMPTOMS

Psychotic episodes are characterized by reality distortion symptoms, known as delusions and hallucinations. Delusions are fixed false beliefs maintained with strong conviction despite clear evidence to the contrary, whereas hallucinations are sensory experiences occurring in the absence of corresponding external stimuli (1). Although commonly discussed in the context of schizophrenia spectrum disorders, these symptoms are transdiagnostic and occur in a variety of psychiatric and neurological disorders, as well as in the context of substance abuse (2).

For decades, impaired dopamine signalling in the midbrain has been considered the central contributor to delusions and hallucinations (3). Dopamine is a widely distributed neurotransmitter, transmitted through four main pathways: the mesocortical pathway (ventral tegmental area to cortex), the mesolimbic pathway (ventral tegmental area to nucleus accumbens), the nigrostriatal pathway (substantia nigra to striatum) and the tuberoinfundibular pathway (hypothalamus to pituitary) (4). Initially, the underlying mechanism was thought to involve an increased number of postsynaptic dopamine receptors, but subsequent studies identified presynaptic dopamine dysregulation as the leading mechanism underlying positive symptoms (3,5). This presynaptic increase in striatal dopamine synthesis and release has formed the theoretical foundation for psychotic symptoms for the past half a century and continues to inform current treatment of delusions and hallucinations.

Since the development of the first antipsychotic medication, chlorpromazine, in 1952, blockade of postsynaptic dopamine D2 receptors in the striatum has been the primary target of antipsychotic pharmacotherapy. Despite the effectiveness of

D2 receptor-blocking therapies, dopaminergic dysfunction provides an incomplete picture of many of the disorders in which psychotic symptoms occur. It is not sufficient to explain complex syndromes such as schizophrenia, where D2 receptor blockade only affects the positive symptom dimension in a meaningful way, while having little effect on what are known as the negative and cognitive symptoms. In addition, despite the strong hereditary components of schizophrenia, genetic studies do not suggest dysfunction of dopamine signalling as the primary cause of the disorder, at least for most individuals (6). Instead, aberrant dopamine signalling is now seen as a final common pathway, where multiple factors such as frontotemporal dysfunction, genetic risk factors, stress and stimulants could converge to give rise to surprisingly similar clinical presentations characterized by positive symptoms (3,6). Other neurotransmitters, including glutamate, serotonin, acetylcholine and histamine, have been suggested to represent upstream regulators of processes leading to schizophrenia.

The shortcomings of the dopamine hypothesis of psychosis are perhaps most clearly seen in two distinct psychotic disorders. Namely, patients with treatment-resistant schizophrenia (TRS) and Parkinson's disease psychosis (PDP) who often either fail to respond to or cannot tolerate commonly used antipsychotic medications. Over the past four decades, no other medication has proved more effective than clozapine, an atypical antipsychotic medication with a relatively low affinity for dopamine receptors, in either condition (7,8). As reflected by numerous negative clinical studies, the dopamine hypothesis of psychosis has ultimately failed to provide both a satisfactory theoretical foundation and novel treatment options for these conditions, and attention is shifting to treatments built on other mechanisms of action. *Table 1* presents the contribution of the most common neurotransmitter systems in both conditions.

Table 1. Proposed contributions of major neurotransmitter systems to schizophrenia, treatment-resistant schizophrenia and psychosis in Parkinson's disease

System	Proposed role in schizophrenia	Role in pathogenesis and treatment of TRS	Role in pathogenesis and treatment of PDP
Dopamine	Increased dopamine synthesis and signalling in mesolimbic pathways, particularly through dopamine D2 receptors, remains central to positive symptoms. Multiple upstream pathologies may converge on a common dopaminergic abnormality.	Striatal dopamine synthesis appears closer to control levels, suggesting a less central role than in treatment-responsive schizophrenia. D2 receptor blockade often insufficient.	Dopaminergic medications contribute to psychosis but do not solely explain it. D2 receptor antagonists can reduce psychotic symptoms but are limited by motor adverse effects.
Acetylcholine	Modulates dopamine signalling mainly through muscarinic M1 and M4 receptors. Role of nicotinic receptors remains incompletely understood.	Role in pathogenesis uncertain. Direct evidence remains limited, but M1/M4 receptor modulation is a potential therapeutic strategy.	Deficits are strongly associated with cognitive and neuropsychiatric symptoms, including psychosis. Pharmacological modulation is a potential therapeutic strategy.
Serotonin	Regulates dopamine signalling in mesocortical and mesolimbic pathways.	Secondary role to glutamate. 5-HT2A modulation is a potential therapeutic strategy.	Important contribution through 5-HT2A receptors. The role of 5-HT1A and 5-HT3 receptors remains less certain. 5-HT2A modulation represents a leading therapeutic strategy.
Glutamate	The NMDA receptor is a key regulator of cortical and subcortical circuits, including dopaminergic signalling in the midbrain. NMDA receptor antagonists produce a more complete schizophrenia-like syndrome than purely dopaminergic agents such as amphetamine.	Leading mechanistic hypothesis and a major focus of therapeutic development.	Role in pathogenesis uncertain.

System	Proposed role in schizophrenia	Role in pathogenesis and treatment of TRS	Role in pathogenesis and treatment of PDP
TAAR1	Regulates monoaminergic signalling, including dopamine and serotonin pathways. Role in psychosis uncertain.	Role in pathogenesis uncertain.	Role in pathogenesis uncertain. Emerging therapeutic strategy.
Histamine	Histaminergic signalling, especially through the H2 receptor, may modulate glutamatergic and dopaminergic neurotransmission, although its role in schizophrenia remains uncertain.	Role in pathogenesis uncertain.	Role in pathogenesis uncertain.

Abbreviations: 5-HT = 5-hydroxytryptamine receptors (serotonin receptors), NMDA = N-methyl-D-aspartate receptor, PDP = Parkinson's disease psychosis, TAAR1 = Trace amine–associated receptor 1, TRS = Treatment-resistant schizophrenia

TREATMENT-RESISTANT SCHIZOPHRENIA

As many as one third of patients diagnosed with schizophrenia do not respond to traditionally used first- and second-generation antipsychotic medications (9). Patients fulfilling the criteria for schizophrenia who do not respond to two different antipsychotic medications used at an adequate dose over 6 weeks should be considered TRS (10), and evaluated for treatment with clozapine. Whether TRS represents a separate disorder from treatment-responsive schizophrenia, or the most severe aspect of the schizophrenia spectrum, remains uncertain (11). In a study by Demjaha et al., TRS patients displayed normal levels of dopamine in the midbrain when measured with radiolabelled DOPA positron emission tomography (12), suggesting a separate mechanism of action and providing an explanation for why these patients do not respond to D2 blockade (13). TRS has also been shown to present as early- and late-onset types, with an estimated 70% of TRS patients being resistant to treatment at onset of symptoms, while the remaining patients develop it as the disease progresses (14,15). It should also be noted that not all treatment-resistant patients respond to clozapine, and that this condition may comprise multiple different disease pathologies (16).

PARKINSON'S DISEASE PSYCHOSIS

Parkinson's disease (PD) is a common neurodegenerative disorder primarily characterized by motor symptoms. While the root cause of the disorder remains unknown, the disease is known to feature widespread accumulation of intracellular aggregated α-synuclein in the brain. Motor symptoms are primarily associated with degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to a decrease in dopaminergic innervation of the basal ganglia (17). In addition to motor symptoms, PD is associated with a wide range of non-motor symptoms, for many of which the pathogenesis is less well understood. Psychotic symptoms, such as hallucinations and paranoid delusions, occur in approximately 40-60% of patients with PD (18,19) and are associated with worse outcomes (20). These symptoms are exacerbated by antiparkinsonian drug therapies such as dopamine agonists and levodopa but cannot be fully explained as adverse effects of these drugs, as PDP was described before the development of levodopa (21). Furthermore, there is conflicting evidence regarding the correlation with antiparkinsonian drug doses, with some studies reporting a correlation (18,22,23), while others do not (24). Initially, high-dose levodopa infusion did not appear to induce these symptoms (25), but more recent evidence suggests that psychotic symptoms occur more frequently during infusion therapies (26). A characteristic feature of PDP is the presence of visual hallucinations. These are often preceded by milder symptoms such as illusions or a sense of presence; and delusions, when occurring, often do so only at the later stages of the disorder (27).

CURRENT PHARMACOLOGICAL LANDSCAPE

THE SUPERIORITY OF CLOZAPINE

Clozapine was developed in the late 1950s (28), less than a decade after the first antipsychotic medication chlorpromazine (29) was introduced to psychiatric care. Initial studies showed promising results with little extrapyramidal side effects (28), but only a few years later it was withdrawn from the market due to multiple cases of fatal agranulocytosis in Finland in the late 1970s (30). It was reintroduced in limited scale under strict laboratory follow-up regime, but only gained widespread interest after two landmark studies in the late

1980s showed that the adverse effects of clozapine could be mitigated through strict laboratory monitoring, and that it was more effective than chlorpromazine in treating patients with schizophrenia (31,32). A decade later, the effectiveness of using clozapine in treating PDP was demonstrated in two randomized controlled studies (RCTs) (33,34). These studies still constitute the foundation of pharmacological treatment for both conditions, as no other medication has been able to surpass the effectiveness of clozapine in either TRS or PDP despite numerous attempts.

Increased dopamine signalling in the midbrain has traditionally been seen as the main mechanism underlying positive symptoms of psychosis, and consequently blockade of the D2 receptor in the striatum has been considered as the main mechanism of action for antipsychotic medications (3). Clozapine is regarded as one of the most potent antipsychotic medications but has a relatively low affinity for the D2 dopamine receptor when compared to other antipsychotic medications (35), making it something of a pharmacological enigma. Clozapine has a broad receptor affinity profile, working as an antagonist or inverse agonist at the dopamine D2 and D4 receptors, the serotonin 5-HT2A and 5-HT3 receptors, the histamine H1 and H2 receptors and the muscarinic M1 receptor, but an agonist at the muscarinic M4 and the serotonin 5-HT1A receptors, as well as a moderate protean agonist at histamine H3 receptor. Its metabolite norclozapine, however, is a full agonist at the M1 receptor. Further, there is evidence suggesting that clozapine partakes in modulation of glutamate metabolism (36). This unique repertoire of receptor affinities has made it difficult to decipher which effects underlie its positive effects (37-39).

Clozapine is associated with several potentially severe side effects, which in addition to agranulocytosis, include myocarditis, paralytic ileus, pneumonia, seizures, venous thromboembolism and significant weight gain. A fourth of patients with schizophrenia on clozapine discontinue the medication, many due to adverse effects. Severe adverse events, such as agranulocytosis, myocarditis and thromboembolism, are relatively rare, affecting only a small minority of patients (40). Longer follow-ups have, however, highlighted the cumulative risk of paralytic ileus and pneumonia, and highlighted these as among the most important causes of clozapine-related mortality during long-term treatment (41). Historically, the risk of agranulocytosis has mandated frequent monitoring of neutrophil counts during clozapine treatment. However, these recommendations have recently been revised as the risk of agranulocytosis is relatively low in patients with stable neutrophil counts. As the risk for agranulocytosis declines markedly after the first years of treatment (42), annual monitoring may be safe for patients without neutropenia after two years of treatment (43). Currently, the European Medicines Agency (EMA) suggests weekly monitoring during the first 18 weeks of treatment, monthly monitoring until the end of the first treatment year, monitoring every 12 weeks during the second year, and annual monitoring after the first two years in patients without neutropenia. These recommendations are currently being implemented in Finland. Reflecting the concerns about these risks and the need for frequent laboratory follow-up, delays in initiating clozapine treatment in TRS are still common (44,45), and clinicians often resort to less effective options in treating PDP (46,47). As clozapine remains markedly underused in PDP, less is known about its safety profile in PDP when compared to TRS (48). While the risk of agranulocytosis does not seem to be dose dependent, the risk of metabolic complications appears to be lower in PDP, where the required dose is often a tenth of that needed in TRS (48,49). In a small follow-up study on 32 PDP patients using clozapine, the main reason for discontinuation of treatment was not the occurrence of adverse events, but the inconvenience of frequent laboratory testing (49).

Since clozapine was developed, numerous attempts have been made to mimic its effects. Despite the development of dozens of dopaminergic antipsychotic drugs over the past four decades, arguably, none of them fully mimics the receptor affinity profile of clozapine, nor has any drug been able to provide equal therapeutic efficacy, especially for TRS and PDP. The atypical or second-generation antipsychotic medications were brought to the market among great anticipation, and while they have become the primary treatment option for psychotic disorders, they have not provided a clear alternative in TRS or PDP. During the past two decades, the focus has shifted from mimicking the full spectrum towards more precise compounds targeting a specific receptor, yet often in a manner similar to clozapine. It should be noted that not all novel treatment options aim to mimic or replace clozapine (50), as many options are non-pharmacological, and many aim to augment the effect of clozapine. But as initiation of clozapine remains one of the key barriers, and delays are associated with worse outcomes (51), a major unmet need is an effective antipsychotic medication for TRS that clinicians feel comfortable prescribing and whose initiation is not delayed due to a fear of side effects. Whether or not this will be the same medication that alleviates psychotic symptoms in PDP without aggravating motor symptoms remains to be seen.

SHORTCOMINGS OF SECOND-GENERATION ANTIPSYCHOTICS IN PDP

The emergence of atypical or second-generation antipsychotic medications in the 1990s sparked a new interest in the treatment of PDP. Whereas the categorization is ambiguous (52), many of the antipsychotic medications developed during the past three decades do display a lower D2 receptor affinity (53), which was theorized to result in a lower risk of extrapyramidal complication — a common side effect of early first-generation antipsychotic medications. In theory, these new medications could provide a similar effect to clozapine, while maintaining the low risk of extrapyramidal symptoms, but without the potentially fatal side effects.

Risperidone, being the first of the novel medications developed, initially showed great promise in PDP. Multiple open-label studies showed improvement in psychotic symptoms with no worsening of motor symptoms (54-57), while others highlighted the risk for motor complications (58,59). A small RCT comparing risperidone to clozapine did not observe significant differences between alleviation of positive symptoms (60). While not statistically significant, motor symptoms improved in the clozapine group while they worsened in the risperidone group. Olanzapine, sharing a more similar receptor affinity profile to clozapine than risperidone (53), was subsequently theorized to have a more favourable side-effect profile. An open-label trial on 15 patients with PDP initially showed a positive response on psychotic symptoms with no motor deterioration (61). Later studies, however, showed a significant negative effect on motor symptoms (62,63), which was later verified in double-blinded RCT studies, both compared to placebo (64,65) and clozapine (66). In a recent meta-analysis, both risperidone and olanzapine were associated with significant extrapyramidal side effects, and neither drug is recommended for use in PDP (7).

Quetiapine was released a few years after risperidone, and more closely mimics clozapine's relatively low D2 receptor affinity and relatively strong antagonism at the 5-HT2A receptor (53). Due to this similarity, quetiapine was hypothesized to mirror the effects of clozapine. Open-label studies (67-73) and studies comparing quetiapine to clozapine (74,75) suggested that quetiapine might be as effective as clozapine in the treatment of PDP. The effectiveness of clozapine could, however, not be replicated in multiple placebo-controlled studies on PDP patients (76-79) or patients with parkinsonism and psychosis (80). Three reviews (81-83) and one meta-analysis (84) analysing the effectiveness of quetiapine have reached the same conclusion: quetiapine is not significantly more effective than placebo in treating PDP. A later version of the meta-analysis, employing a Bayesian network analysis, suggested that quetiapine may be more effective than placebo, but less effective than clozapine (7). Many previous individual studies have not shown a significant worsening of motor function in association with quetiapine, a result supported by the meta-analysis by Iketani et al. (7). Despite the evidence supporting the use of clozapine, most physicians rely on second-generation antipsychotics such as quetiapine or risperidone in the treatment of PDP (46,47). The use of antipsychotic medications in PDP remains controversial since quetiapine is associated with a significant increase in mortality in the elderly (85).

SHORTCOMINGS OF SECOND-GENERATION ANTIPSYCHOTICS IN TRS

Second-generation antipsychotic medications have been extensively studied in TRS patients. The original study by Kane et al. showed statistically significant improvement in both positive and negative symptoms in patients using clozapine when compared to chlorpromazine, a first-generation antipsychotic medication (32). Regarding second-generation antipsychotic medications the situation is less clear. Two meta-analyses published a decade ago reached different conclusions, with results supporting (86) and contradicting (87) the superiority of clozapine when compared to other second-generation antipsychotic medications. Olanzapine, which most closely mimics the receptor affinity profile of clozapine (53), was shown to be at least almost as effective in treating positive and negative symptoms. A more recent meta-analysis reached a similar conclusion: clozapine is more effective in TRS patients than first-generation antipsychotics and seems to be more effective than second-generation antipsychotics other than olanzapine (8). The authors of the meta-analyses highlight limitations, such as many studies being industry sponsored, omitting measurements of plasma levels of clozapine increasing the risk of using inadequate doses of clozapine, and the varying definitions of TRS used in individual studies. Further, it is likely that many of the patients included in the study most likely do not fulfil the widely used Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines for TRS (10). In two critical subgroup analyses of the most recent meta-analysis — when industry-sponsored studies were excluded and when including only double-blinded studies with high doses of clozapine in very treatment resistant patients — clozapine was shown to be more effective than olanzapine (8).

CURRENT GUIDELINES FOR TRS AND PDP FROM A EUROPEAN PERSPECTIVE

At the time of writing, no antipsychotic medications that do not rely on direct D2 blockade have been approved for the treatment of schizophrenia or PDP in Europe. In contrast, in the United States, such approaches have entered clinical use, with xanomeline–trospium recently approved for use in schizophrenia, and pimavanserin being approved for PDP almost a decade ago. For both PDP and TRS, multiple treatment guidelines have been published, reflecting differently on the available evidence. A recent treatment algorithm for PDP from a European perspective — where pimavanserin is not an option — recommends a trial of quetiapine prior to initiating treatment with clozapine (88). Conversely, the TRRIP guidelines for TRS do not make suggestions regarding which two antipsychotic medications should be trialled before clozapine, although this question was discussed and differing viewpoints presented (10). Adhering strictly to the available evidence, one could argue that a trial of quetiapine prior to clozapine in PDP is not supported, and that olanzapine may warrant consideration as one of the two antipsychotics trialled before clozapine in schizophrenia. However, strict adherence to available evidence may not always be feasible in clinical practice. Trials of quetiapine in PDP have generally been small and underpowered; nevertheless, the drug is well tolerated, widely familiar to clinicians and requires minimal laboratory monitoring. Conversely, although recent meta-analyses highlight olanzapine as an alternative to clozapine in TRS, this evidence is constrained by the heterogeneous definition of TRS in these studies and the role of industry sponsorship.

Taken together, olanzapine most closely mimics clozapine both from a pharmacological and clinical perspective but still seems to be less effective than clozapine in TRS (8) and is hindered by motor complications in PDP (7). Ultimately, it seems unlikely that a medication which primarily relies on dopamine receptor antagonism will achieve the same level of efficacy and tolerability as clozapine in these two conditions. Promising multi-receptor modulators such as brilaroxazine, a serotonin-dopamine modulator currently in late-stage development (NCT05184335), continue to be developed and may ultimately prove effective in one or both conditions. However, as with other atypical antipsychotics, it remains uncertain whether they can overcome the limitations associated with dopamine receptor modulation. Consequently, increasing attention has been directed toward medications that selectively target glutamate, serotonin, acetylcholine and histamine receptors. *Table 2* presents those treatment options that have been developed furthest, while the next section describes these and other promising treatment options in detail.

Table 2. Main new medications that do not rely on dopamine D2 receptor blockade developed for the treatment of schizophrenia or PDP

Medication	Mechanism of action	Results from research on patients with schizophrenia	Results from research on patients with TRS	Results from research on patients with PDP
Xanomeline - trospium	M1 and M4 agonist	Phase III: Significant reduction in PANSS score. Approved by the FDA in 2024 for the treatment of schizophrenia in the United States	No RCTs Conflicting results from case reports	No RCTs No case reports
Emraclidine	M4 allosteric modulator	Phase Ib: Significant reduction in total PANSS score Phase IIb: Failed to meet primary endpoint (reduction in PANSS score) in two studies	No RCTs No case reports	No RCTs No case reports
Pimavanserin	5-HT2A antagonist / inverse agonist	Phase II: Significant reduction in NSA-16 score Phase III: Failed to meet primary endpoint (reduction in NSA-16 score)	No RCTs Positive case report series	Phase III: Significant reduction in SAPS-PD. Approved by the FDA in 2016 for the treatment of PDP in the United States Two ongoing RCTs comparing efficacy to quetiapine

Medication	Mechanism of action	Results from research on patients with schizophrenia	Results from research on patients with TRS	Results from research on patients with PDP
Roluperidone	5-HT2A antagonist α1 antagonist σ2 antagonist	Phase IIb: Significant reduction in PANSS negative score Phase III: Numerical but non-significant reduction in PANSS negative score; further Phase III evaluation ongoing	No RCTs No case reports	No RCTs No case reports
Ondansetron	5-HT3 antagonist	Multiple positive RCTs showing reduction in negative symptoms	Two RCTs show reduction in negative symptoms	Positive open-label studies Ongoing RCT
Ulotaront	TAAR1 agonist 5-HT1A agonist	Phase II: Significant reduction in PANSS score Phase III: Failed to meet primary endpoint (reduction in PANSS score) in two studies	No RCTs No case reports	Pilot study: Non-significant reduction in SAPS-PD score when compared to placebo
Iclepertin	GlyT1 inhibitor	Phase II: Significant improvement in MCCB Phase III: Failed to meet primary endpoint (improvement in MCCB) in three studies	No RCTs No case reports	No RCTs No case reports
Bitopertin	GlyT1 inhibitor	Phase II: Significant reduction in PANSS negative score Phase III: Failed to meet primary endpoint (reduction in PANSS negative score) in multiple studies	No RCTs No case reports	No RCTs No case reports
Evenamide	Voltage-gated sodium channel modulator	Phase II&III: Significant reduction in PANSS score in patients with worsening symptoms on stable second-generation antipsychotic medication	Phase II: One-year open-label, rater-blinded study Significant reduction in PANSS score Phase III: Ongoing	No RCTs No case reports

Abbreviations: 5-HT= 5-hydroxytryptamine receptors (serotonin receptors), FDA = Food and Drug Administration, GlyT1 = Glycine transporter type 1, MCCB = MATRICS Consensus Cognitive Battery, M1 and M4 = Muscarinic acetylcholine receptors M1 and M4, NSA-16 = Negative Symptom Assessment-16, PANSS = Positive and Negative Syndrome Scale, PDP = Parkinson's disease psychosis, RCT = Randomized controlled trial, SAPS = Scale for the Assessment of Positive Symptoms, SAPS-PD = Scale for the Assessment of Positive Symptoms - Parkinson's Disease, TAAR1 = Trace amine–associated receptor 1, TRS = Treatment-resistant schizophrenia

NEW PHARMACOLOGICAL TARGETS

GLUTAMATE

Glutamate is the principal excitatory neurotransmitter in the brain, with its actions mediated through fast excitatory AMPA receptors and NMDA receptors, the latter essential for synaptic plasticity. Multiple studies have demonstrated abnormal levels of glutamatergic metabolite levels across schizophrenia spectrum patients compared with control subjects, particularly in brain areas such as the basal ganglia and anterior cingulate cortex (89). Impaired NMDA receptor function has been suggested as one of the main mechanisms leading to an increase in dopamine signalling in the mesolimbic dopamine pathway (90). Moreover, symptoms caused by disruptions of glutamate signalling through the NMDA receptor support a central role for glutamate in the formation of

psychotic symptoms. For example, prolonged use of ketamine, an NMDA receptor antagonist, and autoimmune encephalitis caused by NMDA receptor antibodies can induce syndromes resembling schizophrenia (91). Crucially, these syndromes often present a more complete mimicry of schizophrenia, with negative and cognitive symptoms often present. The NMDA receptor requires simultaneous binding of glutamate and glycine or D-serine to activate (92). Thus, molecules enhancing NMDA receptor function through the glutamate and/or glycine binding sites have been studied. Multiple molecules have shown promising results in schizophrenia, but so far only a few have been trialled specifically in TRS. Furthermore, most novel pharmacological interventions in TRS have been trialled as add-ons to clozapine in cases with inadequate response (93,94).

Glycine has been studied as a potential add-on to antipsychotic treatment in multiple studies. While it does not seem to alleviate symptoms in TRS patients when added to clozapine (95,96), there is evidence of significant reduction in negative symptoms when used in combination with other antipsychotic medications (50). D-Amino acid oxidase (DAAO) inhibitors, which block the breakdown of D-serine, have been highlighted as one potential target for novel therapies. An RCT on the use of sodium benzoate, a DAAO inhibitor, as an add-on to clozapine in TRS patients with inadequate response showed improvement in both positive and negative symptoms (97). Ω-NaBen is a crystalline form of sodium benzoate with a higher central nervous system exposure (98). A Phase II/III study on its efficacy as an add-on to clozapine in TRS is currently ongoing (NCT03094429). Luvadaxistat, a selective DAAO inhibitor, was originally developed to treat Friedreich ataxia but has recently been studied in schizophrenia. A Phase II trial as an add-on to antipsychotic medication (other than clozapine) showed improvement in cognitive symptoms (99), but these results were not replicated in a more recent trial (100), with no further trials ongoing. Neither trial investigated the effectiveness of luvadaxistat in TRS.

Sarcosine is an inhibitor of the type 1 glycine transporter (Glyt1), which increases the synaptic availability of glycine, leading to an augmentation of glutamate binding to the NMDA receptor. Sarcosine was shown to be an effective add-on to antipsychotic treatment in a small placebo-controlled study (101), but these results were not replicated when patients were using clozapine (102). As clozapine itself already modulates glutamate transmission, the negative results in trials investigating the combination of other glutamate agonists with clozapine may reflect a ceiling effect where further glutamate augmentation provides little benefit (103). Supporting this line of thinking, a clinical case report described a positive response to sarcosine in a TRS patient after clozapine had to be discontinued due to myocarditis (104). A placebo-controlled trial on sarcosine in patients with Parkinson's disease dementia showed initial favourable effects on hallucinations, which were, however, not retained at the 8-week follow-up (105). Iclepertin is a selective Glyt1 inhibitor, which initially showed significant reduction in cognitive symptoms in schizophrenia (106). These results were, however, not replicated in Phase III studies (107). Bitopertin, another Glyt1 inhibitor, failed to translate positive Phase II results — which showed a significant reduction in negative symptoms (108) — to larger Phase III trials (109). It seems unlikely that iclepertin or bitopertin will be trialled in either PDP or TRS.

Evenamide —which modulates glutamate release through blockade of voltage-gated sodium channels — is arguably one of the most promising novel pharmacological treatment options in TRS. In the Phase II trial, addition of evenamide to current second-generation antipsychotic treatment, in patients with schizophrenia experiencing worsening symptoms, was associated with a significant reduction in positive symptoms when compared to placebo (110). These results were replicated in a recent Phase III trial (111). Furthermore, in an open-label study, evenamide was well tolerated in TRS patients with minimal side effects and maintained efficacy even after 12 months of use (112). Evenamide appears to be an effective and safe option for treating TRS as an adjunct therapy to second generation antipsychotic medication (including clozapine) (113). A larger Phase III study to assess its efficacy in TRS patients (as defined by the TRRIP guidelines) is currently ongoing (NCT07184619).

Despite promising results in patients with schizophrenia (114), N-acetylcysteine, a glutamate-modulating agent proposed to restore glutamatergic homeostasis by increasing the delivery of cysteine, did not improve outcomes in patients with TRS when combined with clozapine (115).

Levetiracetam binds to the intracellular synaptic vesicular protein 2A, leading to a reduction in excitatory signalling and neuromodulation mainly through reduced glutamate signalling. It is mainly used in patients with epilepsy but has been shown to normalize hippocampal hyperactivity associated with psychosis in schizophrenia (116). Despite psychosis being a known side effect, preliminary results suggest that it could be effective in treating negative and cognitive symptoms in schizophrenia (117), and a placebo-controlled trial in PDP patients is currently ongoing (NCT05824728).

Memantine is an NMDA receptor antagonist used in advanced stages of Alzheimer's disease, often in combination

with an acetylcholinesterase inhibitor (AChEI). Results are mixed, but it seems to be effective in treating negative symptoms in schizophrenia (118) and TRS patients with a suboptimal response to clozapine (119). Unlike other NMDA receptor antagonists such as ketamine, memantine does not seem to induce psychotic symptoms. The reason for this is not fully understood but may be related to a low affinity for the NMDA receptor, rapid dissociation from the receptor, as well as an uncompetitive mechanism of antagonism (120). No trials specifically studying PDP patients have been conducted.

SEROTONIN

Serotonin is synthesized in the raphe nuclei in the brainstem, with widespread connections across the cortex. There are 14 known serotonin receptors, and serotonin has been implicated in multiple neurological conditions (121). Most centrally for psychosis, it is thought to be a central regulator of dopamine signalling in the mesocortical pathway and has thus been strongly linked to the presence of negative and cognitive symptoms. Stimulation of the 5-HT2A receptor has been shown to lead to an increase of dopamine signalling in both the mesocortical and mesolimbic pathways (121), and administration of 5-HT1A agonists increases dopamine function especially in the mesocortical pathway.

Due to the lower risk of motor complications, medications targeting the serotonergic system of the brain have been extensively studied in psychotic disorders during the past two decades. Pimavanserin, a 5-HT2A receptor antagonist/inverse agonist, has been approved for the treatment of PDP in the US (122). Multiple studies show effectiveness when compared to placebo (123,124), and the lack of direct effect on the dopaminergic system results in a low risk for aggravation of motor symptoms when compared to dopamine antagonists (7). Two large studies comparing pimavanserin to quetiapine in PDP are currently ongoing (NCT04373317, CTRI/2022/04/041968). An RCT of pimavanserin in patients with schizophrenia showed a trend towards improvement in negative symptoms (125). However, these findings were not replicated in the Phase III study (126), leading to the termination of research on pimavanserin use in schizophrenia. No randomized studies were conducted specifically in TRS patients, but a case series of 10 patients with refractory psychosis — six of whom had not responded to clozapine — showed a reduction in positive symptoms following treatment with pimavanserin (127). Further support for the role of serotonin in the emergence of negative symptoms comes from studies of roluperidone (MIN-101), an antagonist of 5-HT2A, α1-adrenergic and σ2 receptors. Although it shares serotonergic activity with pimavanserin, antagonism of σ2 receptors may additionally influence signalling in glutamatergic and dopaminergic pathways. Similarly to pimavanserin, promising Phase IIb results (128) were not fully replicated in the subsequent Phase III trial, where the primary endpoint narrowly missed statistical significance (129). Consequently, the Food and Drug Administration (FDA) concluded that there was insufficient evidence to support approval. A new confirmatory Phase III trial was subsequently initiated in 2026 (NCT07565428). Remlifanserin (ACP-204), a selective 5-HTA2 inverse agonist, has recently been developed to treat psychosis in Alzheimer's disease, and a study on dementia with Lewy bodies (DLB) patients with psychotic symptoms is currently ongoing (NCT07029581).

Trace amines are found in low concentrations in the central nervous system and are thought to play a role in the modulation of monoaminergic neurotransmission (130). Thus, the trace amine-associated receptor 1 (TAAR1) has been considered a potential target in schizophrenia, where dysregulation of dopaminergic, serotonergic and glutamatergic signalling has been theorized to underlie the development of psychosis. Ulotaront, a TAAR1 and 5-HT1A agonist, has been shown to be significantly more effective than placebo in treatment of schizophrenia (131), and a pilot study found a non-significant numerical reduction in the severity of PDP when compared to placebo (132). Two Phase III trials in schizophrenia did, however, fail to meet the primary endpoint, possibly in part due to an unusually large reduction in symptoms in the placebo groups. Whether the efficacy of ulotaront is achieved through serotonergic effects or mediated through the TAAR1 receptor is uncertain. Ralmitaront, a selective TAAR1 agonist, failed to show efficacy in a Phase II trial in patients with schizophrenia and further studies do not seem to be planned (NCT04512066).

Ondansetron is a selective 5-HT3 receptor antagonist used primarily as an antiemetic. 5-HT3 receptors have been implicated in the modulation of dopaminergic signalling within the mesolimbic pathway, as well as nicotinic receptor-mediated cholinergic neurotransmission (133). In the 1990s, three open-label studies suggested that ondansetron could be effective in the treatment of PDP (133). Despite these promising initial findings, no randomized controlled trials were conducted for several decades. However, an RCT investigating ondansetron in the treatment of PDP was initiated in 2024 (NCT04167813). In schizophrenia, ondansetron has been shown to reduce negative symptoms in multiple RCTs (134). Similar findings have been shown for TRS, where two RCTs demonstrated a significant reduction in negative symptoms when ondansetron was added to either haloperidol or risperidone (135,136). Nevertheless,

a recent meta-analysis concluded that the available evidence for the use of ondansetron in TRS remains insufficient and highlighted the need for high-quality RCTs (50).

ACETYLCHOLINE

The cholinergic system of the central nervous system originates in the basal forebrain and upper brainstem. The effects of acetylcholine are mediated through fast-acting, ligand-gated nicotinic receptors and G protein-coupled muscarinic receptors (M1-M5), which facilitate slower modulations of neural signalling. Nicotinic receptors in the central nervous system exist in a wide variety of combinations of multiple α and β subunits. Peripheral muscarinic and nicotinic receptors are widely distributed within the autonomic nervous system and in the neuromuscular junctions respectively, giving rise to many of the side effects associated with cholinergic medications.

Widespread changes in the level of both nicotinic and muscarinic receptors have been observed in schizophrenia (137), and the effect of clozapine on muscarinic receptors has been suggested to, at least partially, account for its effectiveness (38). M1 and M4 receptor agonism reduces dopamine signalling in the mesolimbic pathway and could represent a pathophysiological explanation for the emergence of positive symptoms as well as a target for antipsychotic medications (138). The evidence for the involvement of nicotinic receptors in the development of psychosis is less clear (139). Stimulation of nicotinic receptors in the ventral tegmental area seems to increase dopamine signalling in the ventral striatum (140), and nicotine consumption is more prevalent in patients with schizophrenia than in the general population (141). Patients with a recent psychosis show lower availability of the α7 receptor in the hippocampus (142), and multiple α7 receptor agonists are in development, especially for treating cognitive symptoms in schizophrenia (143).

Imbalances in the cholinergic system have also been suggested to underlie the formation of visual hallucinations in PD (144) and DLB (145), which shares both clinical and neuropathological aspects with PD. In addition, the prevalence of psychotic symptoms in PD correlates with cognitive decline (19,24), which has been tightly linked to alterations in the cholinergic system.

Additional support for the targeting of the cholinergic system comes from the recent approval of xanomeline-trospium, a combination of the M1/M4 agonist xanomeline and the peripheral muscarine antagonist trospium, for the treatment of schizophrenia (146,147). This represents the first approval of an antipsychotic drug whose primary mechanism of action is not based on D2 antagonism, marking a major breakthrough in the treatment of psychotic disorders. Currently, there are no ongoing studies assessing its effectiveness in TRS, but a case report described a case of successful use of xanomeline-trospium in a patient with TRS (148). A more recent case series of 20 treatment-resistant patients did not show significant improvements, but most of the patients discontinued the medication due to side effects (149). These in turn, were attributed to factors such as predominance of schizoaffective disorder diagnoses, concurrent use of anticholinergic medication and not taking xanomeline-trospium with food (150). Moreover, xanomeline-trospium is currently being studied in treating psychosis in Alzheimer's disease (NCT06947941) but has not been trialled in PDP. Emraclidine, a selective M4 allosteric modulator, recently failed to meet the primary endpoint in two Phase II trials (NCT05227690, NCT05227703) following a successful placebo-controlled Phase 1b trial (151), which demonstrated significant improvements in positive and negative symptoms in patients with schizophrenia.

Despite evidence supporting a central role of cholinergic dysfunction in the emergence of psychotic symptoms, relatively few studies have examined the use of AChEIs in the treatment of PDP. AChEIs act more broadly on the cholinergic system by increasing the availability of acetylcholine in the synaptic cleft, thereby enhancing signalling though both nicotinic and muscarinic receptors. While donepezil (152) and rivastigmine (153) do not appear to prevent the development nor slow the progression of PDP, three small open-label studies investigating the effect of donepezil and rivastigmine in PDP reported significant improvement in symptom severity (154-156). Similar results have been described in case series (157-159). Furthermore, in DLB, donepezil has been shown to alleviate visual hallucinations (160,161). Notwithstanding, given the tendency toward substantial improvement in placebo groups in previous double-blind studies (83), results from open-label studies should be approached with caution.

HISTAMINE

Among the principal transmitter substances of the brain, histamine is arguably the least well characterized. Histamine-containing neurons originate in the tuberomammillary nucleus (TMN), extend broadly throughout the cortex, and exert their effects through four receptor subtypes, designated H1 through H4 (162). Increased levels of histamine metabolites have been observed in cerebrospinal fluid in patients with schizophrenia, and histamine receptors H1-3 have been suggested to possibly take part in the formation of psychotic symptoms (163).

Following a case report (164) describing a patient with schizophrenia and a peptic ulcer who improved clinically after treatment with famotidine, an H2 antagonist, an open-label trial subsequently showed improvement in 12 subjects with schizophrenia when famotidine was added to current treatment (165). Two RCTs studying the effects of famotidine in TRS patients showed significant amelioration of positive and negative symptoms when compared to placebo (166,167). Despite these promising results, to our knowledge, no follow-up studies have been conducted. Famotidine has not been trialled in PDP. Instead, famotidine has been studied for the treatment of dyskinesias in PD (168). While famotidine did not result in a significant decrease in dyskinesias, it was well tolerated and no significant adverse events were observed.

Both H2 and H3 receptors remain potential therapeutic targets, but enthusiasm for H3 receptor modulation has waned following several negative Phase II studies of H3 inverse agonists for cognitive symptoms in schizophrenia (163). Furthermore, the discontinuation of 40 mg famotidine tablets means that patients would need to take twenty 10 mg tablets daily to reach the 200 mg dose used by Meskanen et al., potentially limiting the feasibility of clinical implementation (167).

CONCLUSIONS AND FUTURE PERSPECTIVES

Arguably, the major challenges associated with clozapine use are not a lack of evidence for its effectiveness, nor solely its side-effect profile, but rather the hesitancy in initiating treatment and structural difficulties in arranging the required laboratory follow-up. Approximately one fifth of patients presenting with a first-episode psychosis will develop TRS (9,169), and a substantial proportion of these patients already exhibit treatment resistance during the first presentation (14). Thus, from a theoretical perspective, as many as one in ten patients with a first-episode psychosis could be candidates for clozapine within the first six months if guidelines were strictly adhered to. In clinical practice, however, initiation is often delayed (44,45), which has been associated with worse outcomes, including increased risk of suicide and less favourable long-term prognosis (51). In PDP, the situation is similar. Clozapine is an unfamiliar drug for many neurologists, and it is possible that many clinics struggle to cope with the intense initial laboratory follow-up that is required. Patients thus end up using medications that are arguably safer and require less monitoring (46,47), but whose efficacy has not been proven and may even be harmful (7,83). Although the evidence supporting the use of clozapine in both conditions has been available for decades, substantial barriers to its implementation persist in clinical practice. Consequently, there remains a clear need for novel treatment options.

Xanomeline-trospium (146) for schizophrenia and pimavanserin for PDP (123) represent the first FDA-approved antipsychotic medications that do not rely on direct D2 receptor blockade. Xanomeline-trospium could potentially be beneficial for patients with TRS or PDP and could warrant pilot studies in these populations. Unfortunately, regarding pimavanserin, all studies on schizophrenia seem to have been halted, and it will most likely not be trialled in TRS in the near future despite promising results from a small case series (127).

Developing novel drug therapies for the treatment of schizophrenia has proved to be extremely difficult. Many promising drugs — such as pimavanserin, roluperidone, bitopertin, iclepertin, ulotaront and emraclidine — have failed to meet primary endpoints in schizophrenia patients in Phase III studies despite encouraging Phase II or Ib studies (106,151,170). For iclepertin and bitopertin, development in patients with schizophrenia appears to have slowed. Clinical trials demonstrated effects primarily on cognitive and negative symptoms rather than positive symptoms (106-108), and it is thus unlikely that they will be pursued in PDP. Roluperidone is currently undergoing a new Phase III trial after narrowly failing to reach statistical significance in the original Phase III trial. Given its serotonergic mechanism, which it shares with that of pimavanserin, it may represent a candidate for the treatment of PDP. Similarly, a new Phase III trial studying ulotaront in patients with schizophrenia is currently ongoing (NCT06894212). A small encouraging pilot study on ulotaront in PDP has been conducted (132), but these results have not yet led to a larger trial. For emraclidine, no trials in PDP have yet been registered, although there could be a theoretical rationale for investigating its efficacy in PDP. Three decades after the original open-label studies of ondansetron in PDP, there is now renewed interest. Positive results from the ongoing RCT could provide a valuable addition to the limited repertoire of pharmacological treatments for PDP.

Clinical trials on novel antipsychotic drugs focus primarily on schizophrenia, and clozapine users and TRS patients are often excluded. Given that TRS may involve pathophysiological mechanisms less directly connected to dopaminergic dysfunction, these failed trials in schizophrenia may risk limiting research into therapies that could benefit this subgroup. The argument could be made that many of these drugs could be considered a candidate for a Phase II trial in TRS. Results from the Phase III study on evenamide are eagerly awaited and could potentially come to form part of the standard of care in TRS patients

who do not fully respond to clozapine. Other glutamatergic treatment options will hopefully emerge in the coming years. The theoretical support for using them in PDP is less strong, but clinical trials may still be warranted. Further studies on the effect of famotidine in TRS have, perhaps somewhat surprisingly, not followed the two positive RCTs. A large multi-centre RCT could be justified based on these findings, but a lack of commercial incentive makes this unlikely in the near future. The research on famotidine in TRS nevertheless highlights the value of clinical observations and case reports, but also underscores the challenges of translating promising signals into large-scale trials in the absence of industry sponsorship.

Arguably, one the largest discrepancies between PDP pathogenesis and clinical trials is the lack of studies on cholinergic medications. There is robust support for abnormal cholinergic signalling underlying the formation of psychosis in PD (144), but so far, no RCTs on treating these symptoms with anticholinergic drugs have been done. While it would be of utmost value to trial xanomeline-trospium in PDP, there is enough support from case reports and open-label studies to warrant an RCT on whether AChEIs could be effective in treating these symptoms. Psychotic symptoms in PD often precedes dementia, and it is likely that these patients would require AChEI treatment within a few years. AChEIs are often well tolerated in these patients, and clinicians have extensive experience with using this class of medication.

Despite great promise from multiple Phase II studies, it should be ensured that patients receive the best possible treatment while the field is awaiting the arrival of possible positive results from Phase III trials. Clozapine is effective in treating PDP (33,34), perhaps more so than pimavanserin (7). The doses required in PDP are lower than those used in TRS, and while agranulocytosis remains a significant risk, other risks such as metabolic complications seem to be less common, and many movement disorder clinics report a clear clinical benefit with low risks of adverse effects (48,49). Further, clozapine seems to be effective in treating rest tremor in PD (48,171). Considering this evidence, it may be advisable for clinics treating patients with PD to either ensure access to the expertise and infrastructure required to initiate clozapine in PDP patients when required, or to establish a clear referral pathway in case a trial of quetiapine is unsuccessful (88).

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SUICIDE MORTALITY IN NON-AFFECTIVE PSYCHOTIC DISORDERS: NATIONWIDE EVIDENCE ON RISK FACTORS AND TEMPORAL PATTERNS

ABSTRACT

Individuals with non-affective psychotic disorders experience substantially higher suicide mortality than the general population, particularly during the early stages of illness. Despite relatively stable suicide rates in the general population in recent years, evidence on temporal trends and the evolution of suicide risk among people with non-affective psychoses remains limited. We examined suicide mortality among individuals with non-affective psychoses by identifying demographic and clinical risk factors, assessing temporal and regional variation and modelling suicide hazard trajectories from first diagnosis. Using nationwide Finnish register data, we followed individuals with non-affective psychotic disorders between 2012 and 2024. Risk factors were examined using survival analysis with time-varying covariates, and suicide hazard trajectories following first diagnosis were estimated among incident cases. During 2012–2024, 1 129 individuals with non-affective psychotic disorders died by suicide. Suicide mortality was substantially higher among men than women and remained largely stable over time, with no clear temporal trend and no statistically significant regional variation. In survival analyses, male sex, younger adult age, acute and transient psychotic disorders, unspecified psychoses, comorbid substance use disorders and depressive disorders were associated with increased suicide risk, whereas the use of residential social care services was associated with a markedly reduced risk. Suicide hazard peaked immediately after first diagnosis, especially among men, and declined sharply during the first two years, continuing to decrease gradually thereafter. Taken together, suicide mortality remained largely stable over time; however, suicide risk among individuals with non-affective psychotic disorders was high and concentrated in identifiable high-risk periods and clinical contexts, indicating substantial potential for prevention. Suicide prevention strategies for people with non-affective psychotic disorders should prioritize early illness phases, timely care during high-risk periods and integrated treatment of substance use disorders. Further research is warranted to better understand factors underlying the potentially protective role of residential social care services.

KEYWORDS: SUICIDE MORTALITY, NON-AFFECTIVE PSYCHOTIC DISORDERS, PSYCHIATRIC EPIDEMIOLOGY, RISK FACTORS, LONGITUDINAL COHORT STUDY, TIME TRENDS, EARLY PSYCHOSIS, NATIONWIDE REGISTERS

INTRODUCTION

Non-affective psychotic disorders are associated with markedly elevated suicide risk, representing one of the leading contributors to premature mortality in this population. A large body of research has demonstrated that people with non-affective psychotic disorders experience substantially higher rates of suicidal thoughts, attempts and deaths compared with the general population. A meta-analysis reported suicide mortality of approximately 4% in first-episode psychosis cohorts with more than ten years of follow-up (1). Elevated suicide risk has been consistently observed among men, and those presenting with comorbid affective symptoms or substance use (2–4).

The early phase of psychotic illness is consistently identified as a period of heightened risk for suicide mortality. Studies of first-episode psychosis report high rates of suicidal ideation, self-harm and suicide mortality shortly after onset of psychosis (5). For example, a UK cohort reported suicide rates of 304 per 100 000 person-years during the first year, which dropped to 127 per 100 000 person-years between 10 and 20 years (6). Risk is also elevated following psychiatric hospitalization across the course of illness (7).

Over the past three decades, suicide mortality has declined in the general population in many countries (8). In Finland, suicide rates fell steadily from the 1990s until approximately 2015–2020, after which the rate has remained relatively stable (9). Despite the long-term reduction in suicide mortality in the general population, there is limited evidence on temporal trends in suicide mortality among people with non-affective psychoses. This evidence gap is especially relevant because, at the same time, psychiatric hospital bed capacity has declined and inpatient stays have shortened (10). Some studies have shown that the suicide rate has declined among people discharged from psychiatric inpatient care (11–13). A Finnish study later showed that the standardized mortality ratio for suicide among individuals with schizophrenia in Finland declined from 11.0 in 1984 to 6.6 in 2014 (14). Understanding these trends is crucial, as they may reflect broad changes in mental health service organization, treatment accessibility and the quality of ongoing care.

In this study, we use nationwide Finnish register data to examine suicide mortality among individuals with non-affective psychoses. Our objectives were to identify demographic and clinical risk factors for suicide, to assess temporal and regional patterns in suicide mortality in Finland, and to quantify suicide hazard trajectories from the first diagnosis to capture how suicide risk evolves during the early and later phases of illness. Together, these analyses provide an up-to-date and detailed overview of suicide mortality and its risk factors in non-affective psychosis.

METHODS

DATA SOURCES AND STUDY POPULATION

The Finnish Quality of Psychosis Care Register (FQPCR) includes all people with at least one diagnosis of non-affective psychotic disorder in the Care Register for Health Care or in the Register of Primary Health Care visits since January 1st, 2010. Non-affective psychotic disorder was defined as either International Classification of Diseases (ICD-10) codes F20-F29 (schizophrenia, schizotypal and delusional disorders) or International Classification of Primary Care (ICPC-2) codes P72 (schizophrenia) or P98 (other psychosis) when assigned by a physician.

Three exclusion criteria were applied: (i) Non-affective psychotic disorder diagnoses assigned before the age of 7 were disregarded; (ii) People with a dementia diagnosis or dementia-related medication before their first non-affective psychotic disorder diagnosis; and (iii) People whose diagnosis had only been assigned during psychiatric hospitalization, but the diagnosis was not confirmed by discharge diagnosis (Holm et al. 2024). People with exclusion criterion (i) and (iii) are included if a non-affective psychotic disorder diagnosis appears later, whereas (ii) is a permanent exclusion criterion. Register data linked to the FQPCR is listed in *Table 1*. The data are updated yearly, including addition of new patients meeting the inclusion criteria.

We used a hierarchical definition for diagnosis, with the one highest in the hierarchy used if present at least once: schizophrenia (ICD-10: F20), schizoaffective disorders (F25), delusional disorders (F22 and F24), acute and transient psychotic disorders (F23), schizotypal disorder (F21), other non-organic psychotic disorders (F28) and unspecified non-organic psychosis (F29).

The quality registry project received permission to use national register data from the Finnish Institute for Health and Welfare (THL). Under Finnish legislation, register-based studies using only administrative data do not require separate ethics committee approval or informed consent.

Table 1. Registers included in the Finnish Quality of Care Register

Register	Description of available data	Years covered
Care Register for Health Care (THL)	Specialized outpatient visits (including dental care), all inpatient care (primary or specialized)	Since 1996
Care Register for Social Welfare (THL)	E.g. supported housing unit stays	Since 1995
Register of Primary Health Care visits (THL)	Primary healthcare visits and dental care	Since 2011
Register for Reimbursements for Prescription Medicines (SII)	All purchases of prescription medicines	Since 1995
Register for Special Reimbursement Right (SII)	Entitlements for special reimbursement for chronic conditions, including non-affective psychosis	Since 1995
Reimbursements for rehabilitation (SII)	Occupational rehabilitation, psychotherapy	Since 1995
Sickness allowances and disability pensions (SII, Finnish Centre for Pensions)	Starting and ending dates for sickness allowances and disability pensions and related diagnoses	Since 1995
Prescription register (SII)	All medication prescriptions	Since 2017
FOLK data (SF) (Socioeconomic information)	Education, employment, family, living arrangements, etc. See https://aineistokatalogi.fi/catalog/studies/a6946178-3c4d-432e-b4bd-7b32b80932af	Since 1996
Mortality statistics (SF)	Causes of death	Since 2010

THL=Finnish Institute for Health and Welfare, SII=Social Insurance Institution, SF=Statistics Finland

STUDY DESIGN AND FOLLOW-UP

Analyses covered the calendar years 2012–2024. Individuals contributed person-time from the later of (a) their first eligible non-affective psychotic disorder diagnosis date, or (b) 1 January 2012. Follow-up continued until 31 December 2024, or death, whichever occurred first. Follow-up was interrupted at emigration and resumed if they subsequently returned to Finland.

We constructed two analysis datasets:

1. Yearly cumulative cohorts of individuals under treatment (for annual suicide mortality rates and Poisson models). A person was considered to be 'under treatment' for the year if they had received treatment for a non-affective psychotic disorder during that calendar year or the two preceding years.
2. The full cohort (2012–2024) with time-updated covariates (for risk factor analyses and cause-specific hazards).

For the analysis of suicide risk following first diagnosis, we restricted the cohort to incident cases whose first eligible diagnosis occurred on or after 1 January 2012, and who did not have a pre-existing special reimbursement right for the treatment of severe mental disorder (code 112) in the Register for Special Reimbursement Right maintained by the Social Insurance Institution of Finland.

OUTCOME

Deaths by suicide were ascertained from the Cause of Death Register maintained by Statistics Finland. The register includes all individuals who have died in Finland as well as persons with a valid Finnish personal identity number who died abroad. The suicides were defined as ICD-10 codes X60–X84 and Y87. During 2012–2024, there were 10,164 deaths from suicide.

COVARIATES

Sociodemographic characteristics, clinical diagnoses and service use were treated as time-varying covariates unless otherwise specified. Sex and age at first eligible psychosis diagnosis were included as fixed sociodemographic covariates.

The primary psychosis diagnosis was treated as a time-varying exposure. At each time point, individuals were assigned to the highest hierarchical psychosis diagnosis they had received up to that date.

Substance use disorders were defined using ICD-10 codes F10–F19, excluding F17 (nicotine dependence) and treated as time-varying covariates. At each time point during follow-up, individuals were considered to have a recent substance use disorder if they had any diagnosis within the preceding five years, a past substance use disorder if they had a substance use disorder diagnosis earlier but not within five years, and no substance use disorder if they had never received such diagnosis. Depressive disorders were also included as time-varying covariates and classified into psychotic depression (F32.3 or F33.3) and non-psychotic depression (F32–F33 excluding psychotic subtypes). Bipolar disorder (F30–F31) was similarly modelled as a time-varying covariate.

Use of residential social care services was included as a time-varying indicator reflecting periods during which individuals lived in supported housing facilities. The data was obtained from the Care Register for Social Welfare. Psychiatric hospitalizations were incorporated in a table as descriptive information. Regional variation was examined across all 22 wellbeing services counties on the Finnish mainland. To account for potential period effects, the COVID-19 pandemic period (the years 2020–2021) was included as an additional binary covariate.

STATISTICAL ANALYSIS

Annual suicide mortality rates per 100 000 person-years were calculated for the calendar years 2012–2024 stratified by sex. Time trends in suicide mortality by sex were examined using Poisson regression with a log link, with the number of suicides as the outcome and the log of person-years as an offset. The model adjusted for calendar year as a continuous variable, sex and an indicator for the COVID-19 period (2020–2021). Rate ratios (RRs) with 95% confidence intervals (CIs) were reported. Regional variation in suicide mortality was examined by aggregating all suicide deaths and person-years across the full follow-up period (2012–2024) for each wellbeing services county. Area-level differences were assessed using a Poisson regression model with the number of deaths as the outcome and the log of person-years as an offset, adjusting for sex. Overall regional variation was evaluated using a likelihood ratio chi-square test from the Poisson model.

Risk factors for suicide were examined using Cox proportional hazards regression in the full cohort. Follow-up time was split into episodes defined by changes in time-varying covariates. The timescale was years since cohort entry. The model included sex and age at cohort entry as fixed baseline covariates, with age grouped into five categories (≤20, 21–35, 36–50, 51–65, >65 years). The hierarchical non-affective psychosis diagnosis, substance use disorders, bipolar disorder, psychotic depression and non-psychotic depression were modelled as time-varying covariates, as was the use of residential social care services.

To characterize the evolution of suicide risk following the first non-affective psychosis diagnosis in incident cases, sex-specific cause-specific hazard functions were estimated using B-spline smoothed hazards, with time since first non-affective psychosis diagnosis as the time axis.

All analyses were performed using R version 4.5.3, with packages including survival, data.table, bshazard, dplyr and ggplot2.

RESULTS

STUDY POPULATION AND DESCRIPTIVE CHARACTERISTICS

During 2012–2024, a total of 1129 individuals with non-affective psychotic disorders died by suicide, corresponding to approximately 11% of all suicide deaths in Finland during 2012–2024 (n=10,164). Their demographic and clinical characteristics differed from those of the remaining population (*Table 2*). Men accounted for two-thirds of suicide deaths, whereas the comparison population had an approximately equal sex distribution. Individuals who died from suicide were more often in younger adult age groups, with 41% aged 21–35 years, compared with 23% in the comparison population.

There were notable differences in diagnostic profiles. Acute and transient psychotic disorders and unspecified non-organic psychoses were more common among those who died by suicide, whereas schizophrenia was less prevalent in this group. Substance use disorders were also markedly over-represented: 48% of those who died from suicide had a lifetime substance use diagnosis, compared with 31% in the comparison population, and substance-related diagnoses within the last 12 months of follow-up were more than twice as common. Psychiatric hospitalization within the last 12 months of follow-up was substantially more common among individuals who died by suicide (64% vs. 29%). Together, these descriptive findings suggest that people who died from suicide were younger, more often male and exhibited higher levels of substance use comorbidity and recent hospital care.

Table 2. Demographic and clinical characteristics of individuals with non-affective psychotic disorders, comparing suicide decedents based on their last year of life with individuals under treatment in 2024

	Description of available data		Comparison population in 2024	
	n	%	*n*	%
Sex				
Men	758	67.4%	28619	51.3%
Women	367	32.6%	27199	48.7%
Age category				
≤ 20	30	2.7%	1760	3.2%
21-35	466	41.4%	13033	23.3%
36-50	313	27.8%	14738	26.4%
51-65	224	19.9%	13330	23.9%
Over 65	92	8.2%	12957	23.2%
Diagnosis				
Schizophrenia	426	37.9%	28630	51.3%
Schizoaffective disorders	104	9.2%	5297	9.5%
Delusional disorders	106	9.4%	6185	11.1%
Acute and transient psychotic disorders	138	12.3%	4065	7.3%
Schizotypal disorder	18	1.6%	837	1.5%
Other non-organic psychotic disorders	10	0.9%	758	1.4%
Unspecified non-organic psychotic disorder	314	27.9%	9975	17.9%
ICPC-2 diagnosis only	9	0.8%	71	0.1%
Diagnosis, within the last 12 months of follow-up				
Non-affective psychosis diagnosis	956	85.0%	42229	75.7%
Other F-diagnosis	87	7.7%	3678	6.6%
No F-diagnosis	82	7.3%	9911	17.8%
Substance use diagnosis, lifetime				
Yes	542	48.2%	17573	31.5%
No	583	51.8%	38245	68.5%
Substance use diagnosis, within the last 12 months of follow-up				
Yes	326	29.0%	6594	11.8%
No	799	71.0%	49224	88.2%

	Description of available data		Comparison population in 2024	
	n	%	*n*	%
Number of hospitalizations, after the index diagnosis				
No hospitalizations	92	8.2%	7041	12.6%
1-5	655	58.2%	28811	51.6%
6 or more	378	33.6%	19966	35.8%
Any hospitalization within the last 12 months of follow-up				
Yes	724	64.4%	16196	29.0%
No	401	35.6%	39622	71.0%
Residential social care services over the lifetime				
Yes	354	31.5%	20875	37.4%
No	771	68.5%	34943	62.6%
Residential social care services, within the last 12 months of follow-up				
Yes	167	14.8%	10802	19.4%
No	958	85.2%	45016	80.6%

TIME TRENDS AND REGIONAL VARIATION

Between 2012 and 2024, suicide mortality among individuals with non-affective psychotic disorders remained largely stable. Crude suicide mortality was substantially higher among men (226 per 100,000 person-years) than among women (112 per 100,000 person-years). *Figure 1* shows the annual suicide mortality rates per 100 000 person-years for men and women. Annual suicide rates showed modest year-to-year fluctuations with no clear pattern. In the adjusted Poisson regression, calendar year was not associated with suicide mortality. Women had 50% lower suicide mortality than men (RR=0.50, 95% CI 0.44–0.56, p<.001). The COVID-19 period was associated with a non-significant reduction in suicide mortality (RR=0.86, 95% CI 0.72–1.02, p=0.10).

Observed crude suicide rates ranged from 42 to 187 per 100 000 person-years among women and from 159 to 316 per 100 000 person-years among men across the wellbeing services counties (*Figure 2*), but these differences did not reach statistical significance ($\chi^2(21)=24.2$, p=0.28).

Figure 1. Annual suicide mortality rates per 100,000 person-years for men and women during the study period

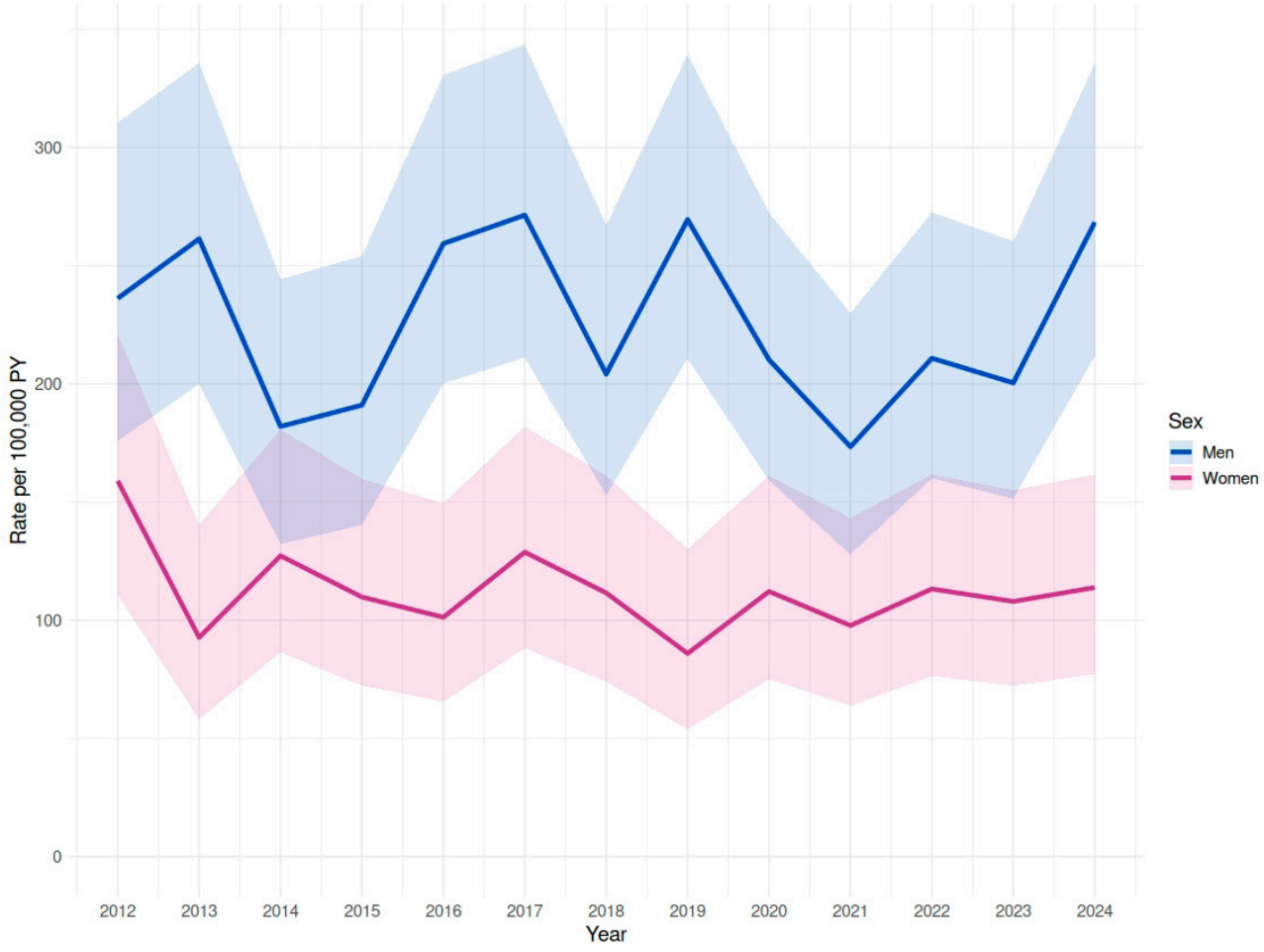
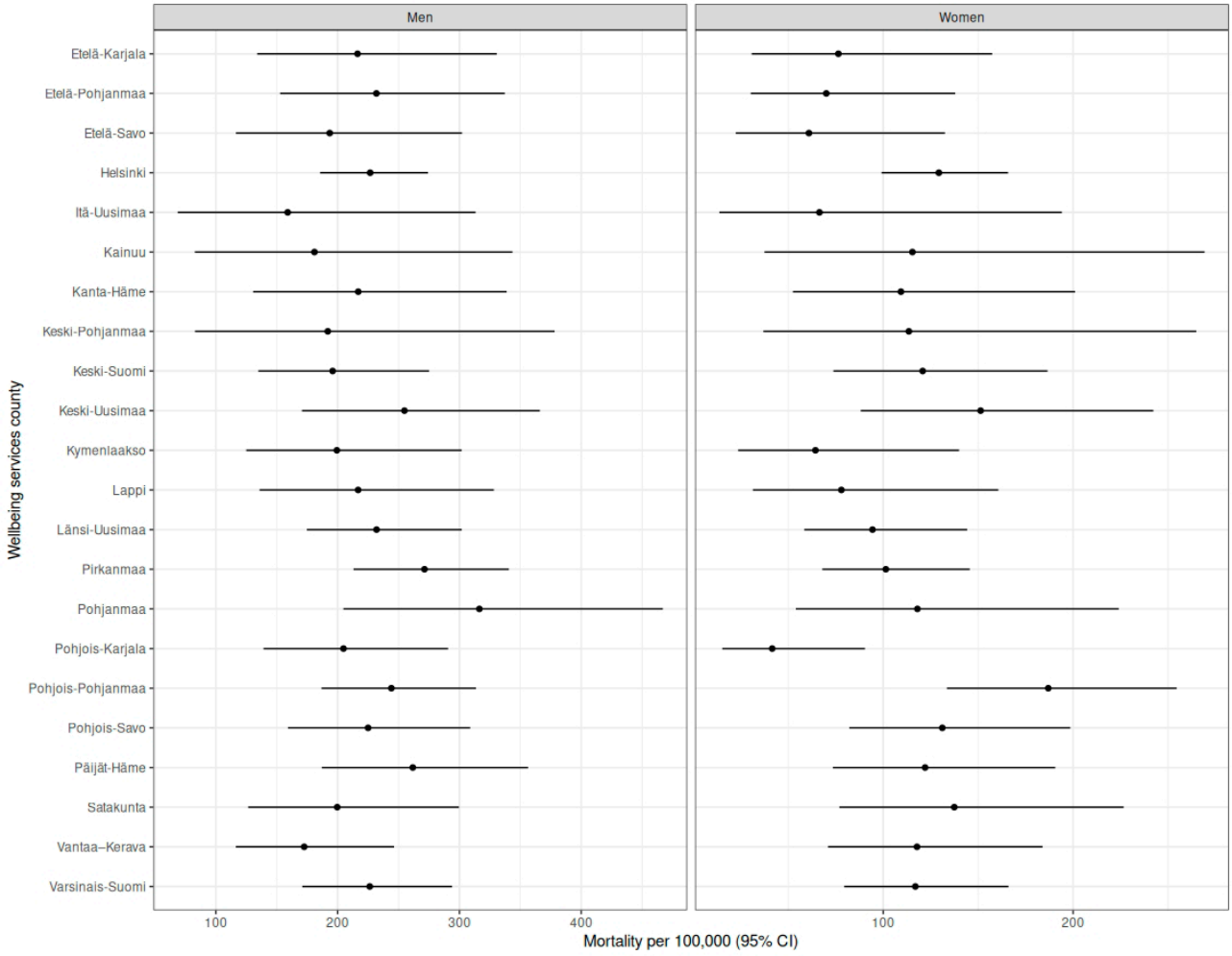


Figure 2. Suicide mortality rates across wellbeing services counties among men and women. Substantial variation in observed rates was seen across counties for both sexes. However, differences did not reach statistical significance ($\chi^2(21)=24.2$, $p=0.28$)



RISK FACTORS FOR SUICIDE

In the multivariable Cox regression model, several demographic and clinical characteristics were associated with suicide mortality among individuals with non-affective psychotic disorders (*Table 3*). Women had a substantially lower hazard of suicide than men (HR=0.51, 95% CI 0.47–0.57). Compared with adults aged 36–50 years, the hazard was higher among those aged 21–35 years (HR=1.18, 95% CI 1.03–1.36).

Compared with schizophrenia, the hazard was elevated for acute and transient psychotic disorders (HR=1.69, 95% CI 1.42–2.02) and unspecified non-organic psychoses (HR=1.51, 95% CI 1.31–1.75). Regarding comorbid conditions, recent substance use disorder diagnosis (HR=2.19, 95% CI 1.94–2.46), past substance use disorder diagnosis (HR=1.52, 95% CI 1.18–1.95), and both psychotic (HR=1.40, 95% CI 1.20–1.64) and non-psychotic depression (HR=1.51, 95% CI 1.33–1.71) were associated with increased hazard. In contrast, residential social care services were associated with a markedly lower hazard of suicide (HR=0.14, 95% CI 0.09–0.21).

Table 3. Multivariable Cox regression analysis of suicide mortality among individuals with non-affective psychotic disorders

Characteristic	HR	95% CI	p-value
Sex	0.51	0.47–0.57	< .001
Age category			
36–50 (ref)	NA	NA	—
Under 20	0.95	0.78–1.15	.59
21–35	1.18	1.03–1.36	.02
51–65	0.95	0.78–1.15	.60
Over 65	0.82	0.60–1.11	.20
Diagnosis			
Schizophrenia (ref)	NA	NA	—
Schizoaffective disorders	1.10	0.88–1.36	.40
Delusional disorders	1.14	0.93–1.40	.22
Acute and transient psychotic disorders	1.69	1.42–2.02	< .001
Schizotypal disorder	0.88	0.61–1.25	.47
Other non-organic psychotic disorders	0.86	0.48–1.53	.61
Unspecified non-organic psychotic disorder	1.51	1.31–1.75	< .001
ICPC-2 diagnosis only	1.68	0.92–3.06	.09
Substance use disorder			
No (ref.)	NA	NA	—
Past	1.52	1.18–1.95	.001
Recent (diagnosis within five years)	2.19	1.94–2.46	< .001
Bipolar disorder	1.10	0.95–1.28	.22
Psychotic Depression	1.40	1.20–1.64	< .001
Non-psychotic Depression	1.51	1.33–1.71	< .001
Residential social care services	0.14	0.09–0.21	< .001

Abbreviations: CI=Confidence Interval, HR=Hazard Ratio

SUICIDE RISK AFTER FIRST DIAGNOSIS

The suicide hazard peaked immediately after the first psychiatric diagnosis for both men and women, with a markedly higher level among men (*Figure 3*). In men, the hazard reached approximately 0.012 per person-year at first diagnosis, whereas among women the peak was substantially lower, about 0.002-0.003. The hazard decreased sharply during the first two years and continued to decline gradually thereafter. By ten years after first diagnosis, the hazards had fallen to around 0.001 in men and below 0.0005 in women. Overall, the results indicate that the suicide risk is highest immediately after first diagnosis, particularly among men, and then declines steadily over time.

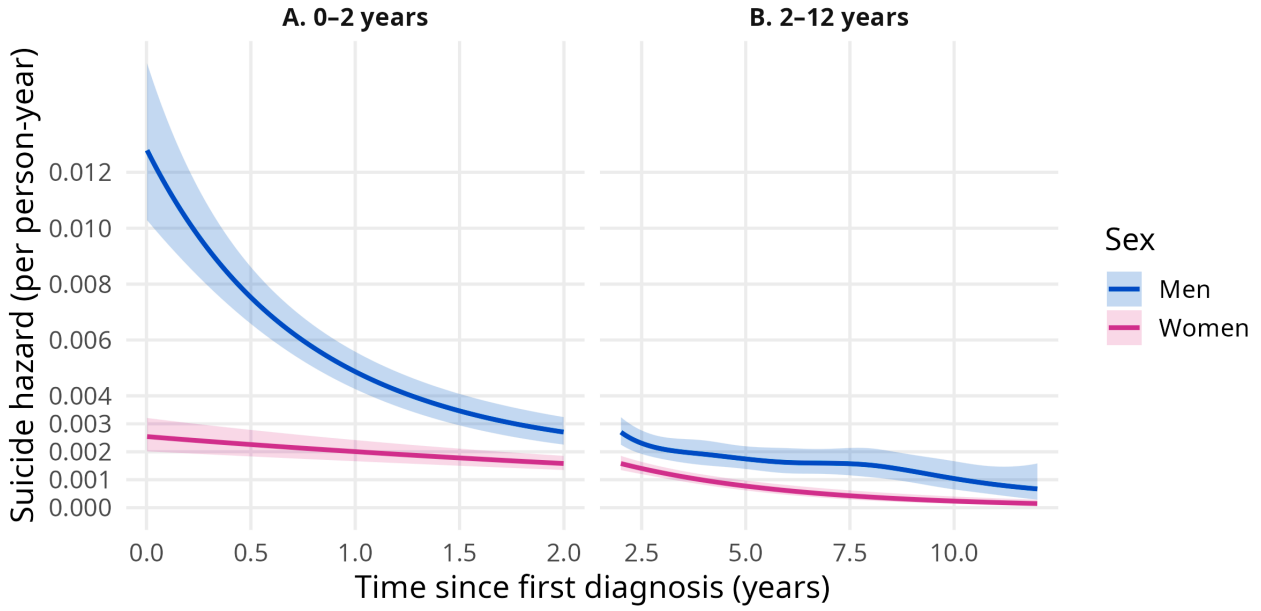
DISCUSSION

In this nationwide register-based study, we examined suicide mortality among individuals with non-affective psychotic disorders in Finland, focusing on demographic and clinical risk factors, temporal and regional variation and suicide hazard trajectories from the time of first diagnosis. Our results show that suicide mortality has remained relatively stable in people with non-affective psychotic disorders over the past decade. Despite this stability, suicide mortality in this population was very high in absolute terms. Compared with the general population, mortality levels were more than ten times higher (9). In addition, our findings provide updated nationwide evidence on the timing and clinical context of suicide risk, largely consistent with international literature and previous Finnish studies (4,15), while also highlighting areas where preventive efforts could be strengthened within the Finnish mental healthcare system.

In Finland, substantial declines in suicide mortality were observed in the general population from the 1990s until around 2015 (9), during which also suicide mortality in people with non-affective psychotic disorders declined (14), followed by a period of stabilization in the general population. Consistent with this pattern, our analyses showed that suicide mortality among individuals with non-affective psychotic disorders has remained largely stable during the study period. The stability of suicide mortality in this population suggests that the potential for further reductions in suicide mortality among individuals with non-affective psychotic disorders may be limited without additional, targeted preventive strategies aimed at this high-risk population.

The first two years after the first diagnosis were associated with the highest risk of suicide mortality, and the risk was particularly high for males. This finding is consistent with earlier research (6,16,17). In addition, suicide risk was higher among young adults, in line with earlier research (4,6). These results emphasize the importance of intensive, multimodal treatment and services and psychosocial interventions for young people with recent-onset psychosis (18,19).

Figure 3. Cause-specific suicide hazard after first psychiatric diagnosis among men and women. Hazard peaks immediately after diagnosis and declines steadily over time



Acute and transient psychotic disorders as well as unspecified psychosis were associated with higher suicide risk. Both diagnoses are commonly used in Finnish psychiatric services for young people with psychotic illness, even after multiple episodes. An area of further study in Finland would be whether a diagnosis suggesting mild or transient psychotic disorder is potentially associated with a risk of less intensive treatment or drop out from treatment.

Both recent and past substance use disorder diagnoses were associated with increased suicide risk, with recent substance use disorder having a larger effect. This result is consistent with several previous studies (2,20,21). A recent report of services for people with severe mental disorders in Finland found that services for people with comorbid psychotic and substance use disorders are currently insufficient in many areas (22). Less than half of the wellbeing services counties had specialized services for these patients in psychiatric inpatient or outpatient services, and providing integrated care was challenging in many areas (22).

Furthermore, having had a diagnosis of mood disorder was associated with increased suicide risk. Depressive symptoms and episodes are an established risk factor for suicide in people with non-affective psychotic disorders (3,5,15,23). This underlines the importance of assessing and treating depression among people with non-affective psychotic disorders.

Recent psychiatric hospitalization was more common in people with non-affective psychotic disorders who had died from suicide than in other cohort members. This association was expected, as suicidality is one indication for psychiatric hospitalization and previous studies have shown elevated suicide risk after discharge from psychiatric inpatient care in individuals with non-affective psychotic disorders as well as transdiagnostically (7,12,23,24). A South Korean study further supports the clinical relevance of the post-discharge period, showing that first outpatient visit within 7 days after discharge was associated with decreased risk of suicide compared to those who had no outpatient visits in the first 30 days after discharge (25). However, timely first outpatient visit may also be a marker of more intensive outpatient treatment and better engagement with services (26).

A novel finding was that stays in residential social care services, including supported housing units, were associated with notably lower suicide risk. The hypothetical mechanisms might be related to having secure living arrangements, social contacts, rehabilitation services, support with treatment adherence and knowledge that professional help is available in the unit if needed. Further research on residential social care services would be very welcome, as there have also been concerns about the quality of these services (27). Future studies should examine the extent to which this association reflects the effects of residential social care services themselves versus differences in the clinical characteristics of patients entering these services, including illness phase, symptom profile and severity of illness.

LIMITATIONS

Diagnostic accuracy is uncertain in register-based research. Furthermore, diagnoses tend to change during the first years of illness, with initial diagnosis of schizophrenia having the highest and acute and transient psychotic disorders the lowest diagnostic stability (28). Thus, individuals who ultimately receive a schizophrenia diagnosis may initially receive less specific psychotic diagnoses. In our hierarchical classification of lifetime diagnoses, these individuals were classified as having schizophrenia. The FQPCR only includes people who have received a diagnosis of non-affective psychotic disorder (ICD-10 diagnostic codes F20-F29), and therefore comparison with substance-induced psychotic disorders and affective psychoses could not be done.

CONCLUSIONS

Despite stable suicide mortality over time, individuals with non-affective psychotic disorders continue to face a substantial risk of suicide. These findings underscore the importance of structured assessment and management of suicide risk throughout illness course, especially at hospital admission as well as around discharge and immediately following the first diagnosis in line with national treatment recommendations (29). Continuity of treatment is a key not only to the good quality of care but also to success in suicide prevention. For young people with recent-onset psychosis, intensive, multimodal treatment, services and psychosocial interventions are needed. Further declines may be achieved by actively addressing modifiable risk factors within this population, such as substance use comorbidity, depressive symptoms or hopelessness emerging from social difficulties and societal alienation.

Conflict of Interest

None

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SUBSTANCE USE PROFILES IN FIRST-EPISODE PSYCHOSIS AND PSYCHOSIS-RISK PATIENTS - RESULTS OF THE TURKU EARLY PSYCHOSIS STUDY (TEPS)

ABSTRACT

***Background**: Substance use is known to be prevalent in first-episode psychosis (FEP). Substance use is also a known risk factor for psychosis in vulnerable individuals and forms one of the treatment targets in preventive early intervention protocols. **Aims**: The aim of this study was to evaluate prevalence and detailed characteristics of substance use profiles in patients with FEP and patients with a clinical psychosis risk compared to those in a general population sample. **Method**: The sample consisted of in- and outpatients recruited from the psychiatric services in South West Finland between years 2011 and 2017. The participants were divided into four groups based on standardized clinical evaluation: 1) patients with FEP (n=130); 2) patients with clinical high risk for psychosis (CHR-P) assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS) (n=61); 3) patients with clinical psychosis risk assessed by the clinical treatment team but not fulfilling the SIPS criteria (CHR-N) (n=44); and 4) general population controls (n=121). Past and current substance use data was collected using questionnaires. **Results**: Across all study groups, current regular cigarette smoking, hazardous alcohol use and illicit drug use during lifetime and during the past 12 months was most common in the FEP group. Lifetime and past 12 months cannabis use was significantly more common only in the FEP group compared to the control group. However, other illicit drug use during both lifetime and past 12 months was more common in all patient groups compared to the control group. While current regular smoking was more common in all patient groups compared to the control group, hazardous alcohol use defined as AUDIT score ≥8 points was not. **Conclusions**: Substance use is highly prevalent in first-episode psychosis and in patients with a clinically defined risk for psychosis. Thus, detailed screening of substance use in this vulnerable population is an important clinical priority in integrated early intervention strategies aimed at improving patient outcomes.*

KEYWORDS: FIRST-EPISODE PSYCHOSIS, CLINICAL HIGH RISK FOR PSYCHOSIS, SUBSTANCE USE, ALCOHOL USE, TOBACCO, CANNABIS

INTRODUCTION

Substance use is remarkably common among first-episode psychosis (FEP) patients; tobacco, alcohol and cannabis being the most frequently used substances (1–3). Substance use is an established adverse prognostic marker for FEP patients, as this comorbidity has been associated with various adverse outcomes including medication non-adherence (4), severity of symptoms (5) and frequent service use (5). However, research examining substance use of patients at clinical high-risk (CHR) for psychosis is limited and the literature is dominated by research on cannabis use. In the meta-analysis of Kraan et al., cannabis use disorder but not cannabis use was associated with transition to psychosis (6). As well, findings from population-based studies suggest the use of tobacco (7), cannabis (8) and inhalants (9), but not alcohol (10), to be associated with increased risk for subsequent psychotic disorders. Tobacco and cannabis have also been associated with earlier age of onset of FEP (1,11).

In previous studies, more than half of the FEP patients have been estimated to smoke cigarettes daily (12). Prevalence of current and lifetime use of cannabis has been estimated to be 30% and at least 50%, respectively (2,3). For other illicit drug use, estimates for current and lifetime prevalence have

been considerably higher among FEP patients compared to the general population (3,13,14). In addition, hazardous alcohol use and alcohol use disorder (AUD) are reported to be a common comorbidity among this group (13).

While substance use is known to be remarkably common among FEP patients, there is less literature about substance use frequency among CHR patients. Cigarette smoking has been reported to be more frequent among them compared to the controls, approximately one out of three CHR patients being a daily smoker (15). The prevalence of current and lifetime use of cannabis seems to be as common among CHR patients as among FEP patients (16). Research on other illicit drug use among CHR patients is limited, with the existing evidence base suggesting it to be rare (17). Studies also suggest that prevalence of comorbid AUD is high (reaching up to 38%) among CHR patients (15). On the other hand, previous studies have rarely compared alcohol use patterns of CHR patients with healthy controls (15,17).

There is a paucity of studies assessing the prevalence of substance use among Finnish FEP patients or those at clinically high-risk for psychosis, while substance use habits of patients with other psychotic disorders have been examined thoroughly. To our knowledge, there is only one clinical sample-based study addressing the issue of cannabis use and one of alcohol use among Finnish FEP patients. In the study of Karpov et al., prevalence of cannabis use among FEP patients (n=91) in the University Hospital District of Helsinki and Uusimaa was 26% during the past year and 19% during lifetime without recent use (16). Information on other substance use was not collected in that study. In a study of Talonen et al., self-reported alcohol abuse among Finnish adolescent FEP patients was relatively high: 52.8% (n=19) among male and 28.6% among female patients (n=20) (18). As far as we know, there is only one study examining the prevalence of substance use in Finnish patients at high risk for psychosis. In a study by Korkeila et al., self-reported alcohol abuse during lifetime was found to be more common among CHR patients (28%) compared to the controls (8%), as well as substance use disorder (SUD) with prevalence of 23% compared to 7%, respectively (19). In that study, most used illicit drugs were cannabis and amphetamine, but exact prevalence numbers were not provided.

The aim of our study was to assess the prevalence of cigarette smoking, alcohol, cannabis and other illicit drug use during lifetime and past 12 months among FEP and CHR patients from psychiatric services in South West Finland during 2011-2017.

PARTICIPANTS AND METHODS

PARTICIPANTS

The Turku Early Psychosis study (TEPS) (20) is a part of the larger VAMI project (Vakavien Mielenterveyshäiriöiden etiologia ja hoito – research programme; the Aetiology and Treatment of Severe Mental Health Disorders – research programme). The TEPS project includes in- or outpatients from the psychiatric clinics of the City of Turku and the Hospital district of South West Finland with their first psychiatric treatment contact due to psychotic symptoms. The recruitment phase was carried out between October 2011 and December 2017.

Eligible participants were screened to determine if they were psychotic or at high risk for psychosis as determined by the treating clinical psychiatry team. First-episode psychosis was assessed with Structured Clinical Interview for Diagnostic and Statistical Manual for Mental Disorders 4th ed. text revision (Axis-I disorders, SCID-I) according to DSM-IV criteria, including schizophrenia, delusional and bipolar psychoses, acute transient psychoses and other psychoses. Patients with a previous psychotic disorder and IQ <70 were excluded (Wechsler Adult Intelligence Scale vocabulary test performance was used as a proxy for IQ in this study). Clinical high-risk psychosis was defined using the Structured Interview for Prodromal Syndromes version 5.0 (SIPS) category of prodromal syndromes criteria (COPS). Participants fulfilling these criteria form the CHR-P group (21). The other high-risk group was composed of participants who were originally assessed to have clinical features related to psychosis risk in an everyday standard clinical evaluation, but did not quite fulfil the formal SIPS/SOPS criteria. They form the CHR-N group. For the general population control group, through the Turku University Hospital, people were randomly identified from the population register who, based on their age, gender and place of residence, matched the patients included in the study. More detailed information about recruitment protocol and baseline examination is described in previous article (20).

In all, our study included 356 participants who were divided into four groups based on psychosis rate: patients with the first-episode psychosis (FEP, n=130), patients with clinical high risk for psychosis, defined with SIPS/SOPS (CHR-P, n=61), patients who didn't fulfil SIPS/SOPS criteria (CHR-N, n=44) and general population controls (GPC, n=121).

This study was performed in compliance with the 6th revision of the Declaration of Helsinki. The research plan was approved by the Ethics Committee of South West Finland (diary

numbers 64/180/2011 and 65/1801/2013) respectively. All participants gave written informed consent before participation. Capacity to consent was assessed by the patient's responsible clinician.

INFORMATION ON SUBSTANCE USE

Information concerning self-reported substance use was collected using questionnaires.

History of cigarette smoking was questioned as "*Have you ever smoked more than 5 packs of cigarettes during your lifetime?*" with answering options yes or no. Information about current regular smoking was investigated with a question "*Do you still smoke cigarettes regularly?*" with answering options yes or no. In addition, an average number of daily smoked cigarettes was asked with options *1-2, 3-5, 6-10, 11-15, 16-19, 20-25, 26-39* and *40 or more*. Answers were divided into two groups: 1) light daily smoking, i.e. smoking 1-19 cigarettes a day and 2) heavy daily smoking, i.e. smoking at least one pack (20 cigarettes) a day.

Alcohol use was assessed using the ten-item Alcohol Use Disorders Identification Test (AUDIT) since it has been examined to be valid among people with schizophrenia (22) and first-episode psychosis (23). As in previously cited studies, AUDIT score ≥8 points was used as a cut-off value to indicate hazardous alcohol use.

Besides the total AUDIT score value, answers for the first three questions were analysed in the results. The first question was "*How often do you have a drink containing alcohol?*" with answering options *never, monthly or less, 2-4 times a month, 2-3 times a week* and *4 times a week or more often*. The second question was "*How many drinks containing alcohol do you have on a typical day when you are drinking?*" with options *1 or 2, 3 or 4, 5 or 6, 7-9* and *10 or more*. For the statistical analysis, answers were grouped into three categories: 1-4, 5-9 and 10 or more. The third question – an indicator for binge drinking – was "*How often do you have six or more drinks on one occasion?*" with options *never, less than monthly, monthly, weekly*, and *daily or almost daily*. For the statistical analyses, two last answering options were grouped.

The questionnaire included also questions concerning self-reported illicit drug use, namely cannabis, MDMA, amphetamine or methamphetamine, cocaine or crack, heroine or morphine, buprenorphine, other central nervous system (CNS) drugs, LSD or other hallucinogens and inhalant use. In addition, the participants were allowed to report if they had used some other drug not mentioned above. The answering options in the questionnaire were *never, 1-5 times, 6-10 times, 11-50 times* and *50 or more times*. Substance use was examined for both during lifetime and past 12 months. Information on illicit drug use other than cannabis was pooled for the statistical analysis.

STATISTICAL ANALYSES

Statistical analyses were done using the IBM SPSS Statistics 25. Descriptive analyses were performed to establish background characteristics and substance use patterns of the participants. The reported background characteristics included gender (males, females), age (in years), occupation (employed/student, unemployed/incapacitated) and marital status (married/common-law, other).

Multinomial logistic regression analysis was used to compare tobacco, alcohol and illicit drug use of the FEP, CHR-P and CHR-N groups to the GPC group (General population comparison group). The results were reported with odds ratios (OR), corresponding 95% confidence intervals (CI) and p-values, setting the statistical significance at $p<0.05$.

RESULTS

BACKGROUND CHARACTERISTICS

The mean age (years) of all participants was 26.6 with a standard deviation (SD) of 6.2 and ranging from 18 to 49. Of all participants, 52.5% (n=187) were male and 47.5% (n=169) female. Proportion of unemployed or incapacitated ranged from 27.3% to 34.4% in the FEP, CHR-P and CHR-N groups, while 96.7% of the general population controls were employed or students. Less than 30% of the participants in the FEP, CHR-P and CHR-N groups were married or in common-law marriage, while the corresponding percentage in the GPC group was 70.2%. More detailed information about the background characteristics of the participants is reported in *Table 1*.

Table 1. Background characteristics of the participants

	FEP n=130		CHR-P n=61		CHR-N n=44		GPC n=121	
Age, years	mean	SD	mean	SD	mean	SD	mean	SD
	26.6	5.9	25.0	6.2	27.1	8.1	27.4	5.6
Gender	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Male	73	56.2	32	52.5	22	50.0	60	49.6
Female	57	43.8	29	47.5	22	50.0	61	50.4
Basic education								
Comprehensive school or less	52	40.0	26	42.6	21	47.7	21	17.6
General upper secondary education	78	60.0	35	57.4	23	52.3	98	82.4
Professional education								
None	57	43.8	30	49.2	19	43.2	31	26.1
Vocational school	54	41.5	26	42.6	19	43.2	34	28.6
University	19	14.6	5	8.2	6	13.6	54	45.4
Occupation								
Employed or student	72	55.4	29	47.5	23	52.3	117	96.7
Unemployed or incapacitated	37	28.5	21	34.4	12	27.3	1	0.8
Other	21	16.2	11	18	9	20.5	3	2.5
Marital status								
Married or common-law or common-law	31	23.8	17	27.9	13	29.5	85	70.2
Other	99	76.2	44	72.1	31	70.5	36	29.8

SUBSTANCE USE

Cigarette smoking

Information about cigarette smoking is described in Table 2. Current regular tobacco smokers represented 61.7% in the FEP group, 37.5% in the CHR-P group, 47.1% in the CHR-N group and 14.9% in the GPC group. Current regular smoking was significantly more likely in the FEP group (OR: 9.2, 95% CI: 3.4-24.9, p<0.001), in the CHR-P group (OR: 3.4, 95% CI: 1.1-10.9, p=0.036) and in the CHR-N group (OR: 5.1, 95% CI: 1.5-17.7, p=0.011) compared to the general population controls. History of smoking (>5 packs of cigarettes) didn't differ in any group compared to the control group. Heavy daily smoking, i.e. smoking at least 20 cigarettes per day, was more prevalent among the FEP patients (21.9%) compared to other groups (CHR-P 9 %, CHR-N 15.4 %, and 0% in the GPC).

Alcohol

Alcohol use variables, assessed with the ten-question AUDIT questionnaire, among participants are described in *Table 2*. Prevalence of hazardous alcohol use, defined as AUDIT score ≥8 points ranged from 32.7% to 40.0%. The proportion of those who exceeded that score did not differ in any group compared to the control group. When asked the alcohol use frequency,

the highest proportion of the FEP group (n=53, 50.5%) and the CHR-P group (n=20, 40.8%) reported drinking once a month or more rarely, while in the control group, the highest proportion (n=52, 47.3%) were used to drinking 2-3 times per week. However, participants in the FEP group (OR: 4.9, 95% CI: 1.6-15.4, p=0.006) as well as CHR-N group (OR: 5.1, 95% CI: 1.3-19, p=0.017), but not CHR-P group, were more likely to consume 10 units or more during one drinking session, even though when questioning frequency of binge drinking results do not suggest higher frequencies among them.

Illicit drug use

In all groups, the most used illicit drug both during lifetime and past 12 months was cannabis, followed by CNS drugs. MDMA was the third most used illicit drug during lifetime, while amphetamine was the third most frequently used illicit drug during the past 12 months (See *Figures 1-2* and *Table 3*).

Cannabis use

In all, prevalence of cannabis use during lifetime ranged from 40.0% (CHR-N group) to 61.5% (FEP group), and cannabis use during past 12 months from 12.5% (CHR-N group) to 37.1% (FEP group). Prevalence of heavy use (>50 times) ranged from 4.5% (GPC group) to 23.1% (FEP group).

Compared to the GPC group, both lifetime cannabis use (OR: 2, 95% CI: 1.2-3.4, p=0.013) and cannabis use during the past 12 months (OR: 2.3, 95% CI: 1.3-4.3, p=0.007) was more prevalent only in the FEP group.

Other types of illicit drug use

In all, prevalence of other illicit drug use than cannabis ranged from 12.7% (GPC group) to 42.9% (FEP group) during lifetime, and from 4.6% (GPC group) to 27.9% (FEP group) during past 12 months.

The use of other illicit drugs during lifetime was more likely in the FEP group (OR: 5.1, 95% CI: 2.6-10.2, p<0.001), in the CHR-P group (OR: 4, 95% CI: 1.8-9.0, p=0.001) and in the CHR-N group (OR: 4.1, 95% CI: 1.8-9.6, p<0.001) when compared to the GPC group. The use of other illicit drugs during the past 12 months was more likely in all patient groups when compared to the GPC group: the FEP group (OR: 8, 95% CI: 3-21.7, p<0.001), the CHR-P group (OR: 4.8, 95% CI: 1.5-15.2, p=0.008) and the CHR-N group (OR: 4.4, 95% CI: 1.3-14.8, p=0.016).

Table 2. Alcohol and tobacco use among VAMI participants compared to general population controls

	GPC		FEP					CHR-P					CHR-N				
	n	*%*	*n*	*%*	*OR*	*95% CI*	*p-value*	*n*	*%*	*OR*	*95% CI*	*p-value*	*n*	*%*	*OR*	*95% CI*	*p-value*
Alcohol use frequency																	
Never	5	4.5	12	11.4	2.7	0.9-8.0	0.070	11	22.4	6.1	2.0-19	**0.002**	5	12.8	3.1	0.8-11.3	0.09
Once a month or more rarely	36	32.7	53	50.5	2.1	1.2-3.6	**0.009**	20	40.8	1.4	0.7-2.8	0.33	17	43.6	1.6	0.8-3.4	0.23
2-4 times a month	52	47.3	34	32.4	0.5	0.3-0.9	**0.03**	17	34.7	0.6	0.3-1.2	0.14	14	35.9	0.6	0.3-1.3	0.22
2-3 times a week	15	13.6	3	2.9	0.2	0.05-0.6	**0.01**	0	0				3	7.7	0.5	0.1-1.9	0.33
4 times a week or more	2	1.8	3	2.9	1.6	0.3-9.7	0.62	1	2	1.1	0.1-12.7	0.92	0	0			
Usual number of units consumed per drinking session																	
1-4 units	66	62.9	52	56.5	0.8	0.4-1.4	0.37	21	53.8	0.7	0.3-1.5	0.327	19	52.8	0.66	0.3-1.4	0.29
5-9 units	35	33.3	25	27.1	0.7	0.4-1.4	0.35	13	33.3	1.0	0.5-2.2	1.000	11	30.6	0.88	0.4-2.0	0.76
10 units or more	4	3.8	15	16.3	4.9	1.6-15.4	**0.006**	5	12.8	3.7	0.9-14.6	0.061	6	16.7	5.1	1.3-19	**0.017**
Frequency of binge drinking																	
Never	19	17.8	26	26.8	1.7	0.9-3.3	0.12	13	31	2.1	0.9-4.7	0.081	10	25	1.5	0.6-3.7	0.33
Less than monthly	40	37.4	42	43.3	1.3	0.7-2.2	0.39	17	40.5	1.1	0.5-2.4	0.72	16	40	1.1	0.5-2.4	0.77
Monthly	40	37.4	22	22.7	0.49	0.3-0.9	**0.024**	9	21.4	0.46	0.2-1.1	0.066	9	22.5	0.49	0.2-1.1	0.092
Weekly	8	7.5	7	7.2	0.96	0.3-2.8	0.94	3	7.1	0.95	0.2-3.8	0.94	5	12.5	1.8	0.5-5.8	0.34
AUDIT score 8 or more	36	32.7	40	38.1	1.3	0.7-2.2	0.41	17	34.7	1.1	0.5-2.2	0.81	16	40	1.4	0.6-2.9	0.41
Cigarette smoking																	
Ever smoking (>5 packs of cigarettes)	50	45.5	60	57.1	1.6	0.9-2.7	0.087	25	51	1.3	0.6-2.5	0.52	22	55	1.5	0.7-3.0	0.30
Current regular smoking	7	14.9	29	61.7	9.2	3.4-24.9	**<0.001**	9	37.5	3.4	1.1-10.9	**0.036**	8	47.1	5.1	1.5-17.7	**0.01**

Table 3. Drug use during lifetime and past 12 months among VAMI participants compared to general population controls

	GPC		FEP					CHR-P					CHR-N				
	n	*%*	*n*	*%*	*OR*	*95% CI*	*p-value*	*n*	*%*	*OR*	*95% CI*	*p-value*	*n*	*%*	*OR*	*95% CI*	*p-value*
Cannabis use during lifetime	49	44.5	64	61.5	2	**1.2-3.4**	**0.013**	24	49	1.2	0.6-2.3	0.605	16	40	0.8	0.4-1.7	0.620
Other drug use during lifetime	14	12.7	45	42.9	5.1	**2.6-10.2**	**<0.001**	18	36.7	4	**1.8-9**	**0.001**	15	37.5	4.1	**1.8-9.6**	**0.000**
Cannabis use during past 12 months	22	20.2	39	37.1	2.3	**1.3-4.3**	**0.007**	12	25	1.3	0.6-2.9	0.500	5	12.5	0.6	0.2-1.6	0.285
Other drug use during past 12 months	5	4.6	29	27.9	8	**3-21.7**	**<0.001**	9	18.8	4.8	**1.5-15.2**	**0.008**	7	17.5	4.4	**1.3-14.8**	**0.016**

Figure 1. Drug use (%) during lifetime

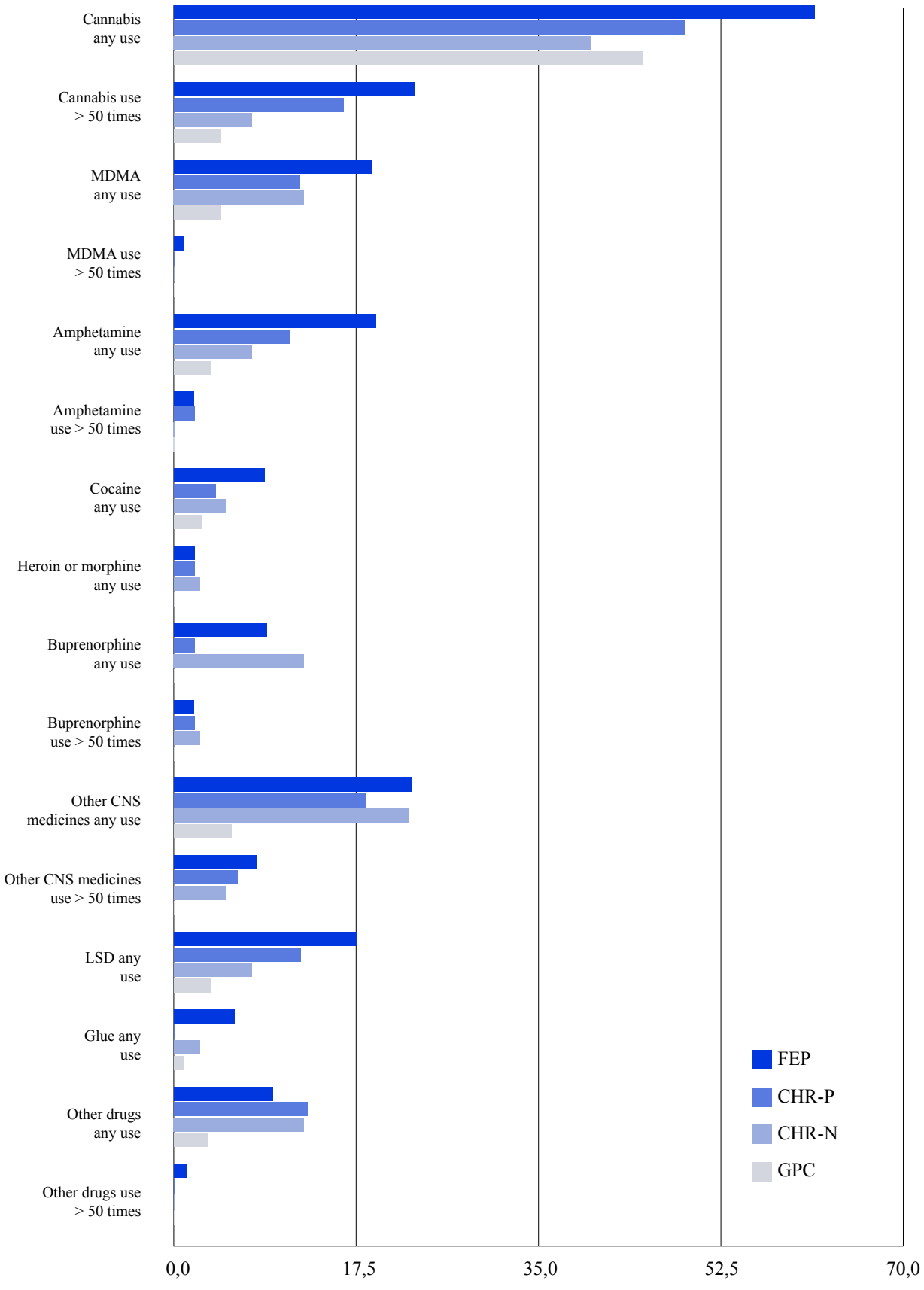
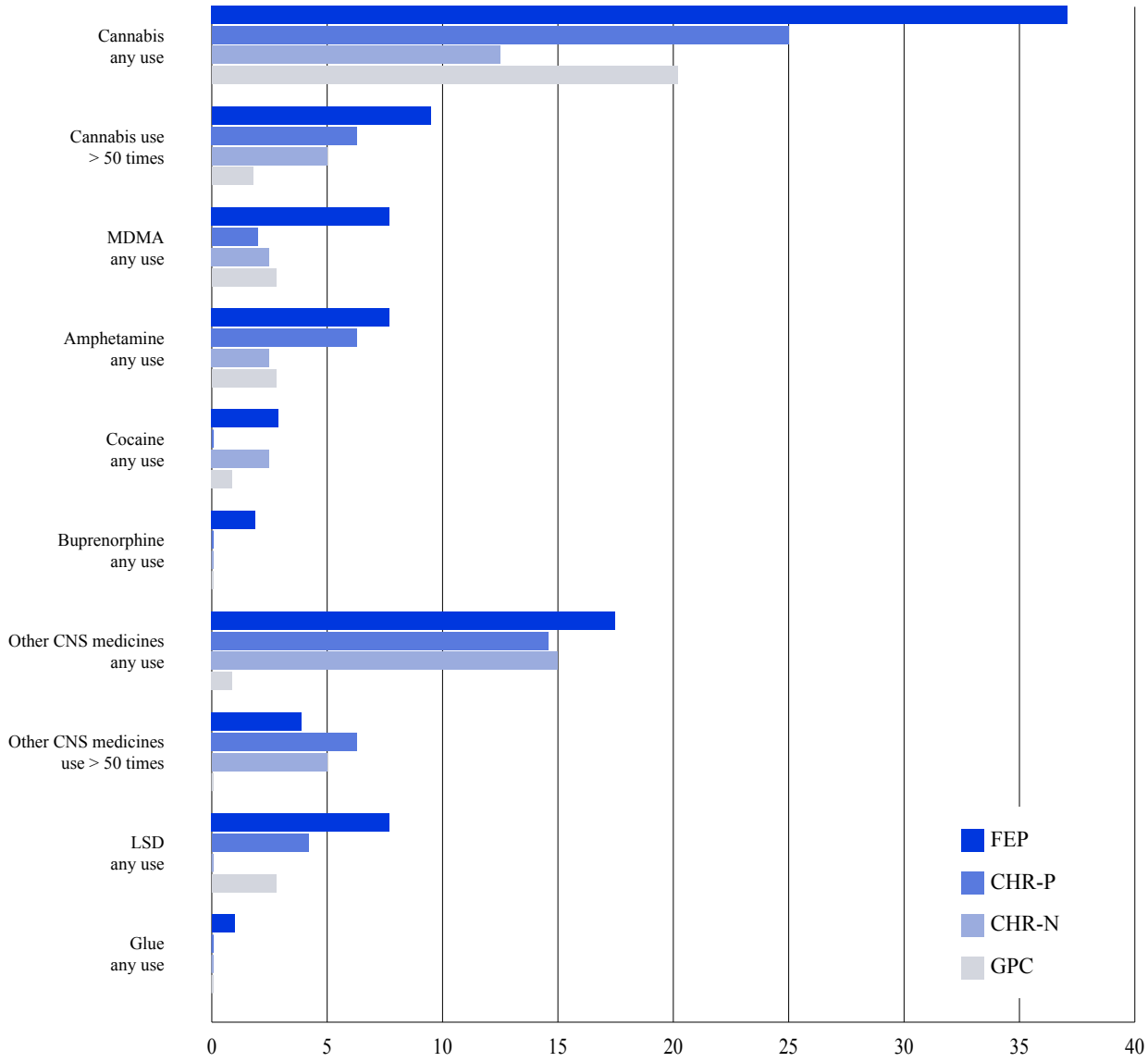


Figure 2. Drug use (%) during past 12 months



DISCUSSION

This study examined prevalence of substance use in a Finnish sample of first-episode psychosis (FEP) and psychosis risk patients (CHR-P and CHR-N), compared to general population (GPC). The key finding was the consistently higher burden of substance use among persons with FEP and in terms of current regular smoking, hazardous alcohol use and illicit drug use (both lifetime and past 12 months). Notably, cannabis use was more common in persons with FEP than in the general population, whereas this difference was not observed in the other patient groups. Although current regular smoking was more common in all patient groups than in general population controls, hazardous alcohol use was not.

Even though prevalence of substance use in psychosis risk patients was not as high as in FEP patients, it was still notably common. When compared to general population, cigarette smoking and illicit drug use except cannabis were more common among them; also, the pattern was the same regardless of whether psychosis risk assessment was made with structured interview or not.

Consistent with a meta-analysis by Myles et al., more than half of the FEP patients in our sample reported current regular cigarette smoking. Among the participants in the CHR-P and CHR-N groups, prevalence was not as high (37.5% and 47.1%), although significantly higher than in the control group (14.9%) and substantially similar as that reported in previous studies (15). Previous literature provides limited information about smoking among Finnish FEP or high-risk patients, yet three Finnish studies with schizophrenia patients proposed approximately 44% for self-reported daily smoking (24–26). Interestingly, in two of these studies the prevalence of daily smoking was lower, below 30% among people with affective or other non-affective psychosis (24,25). Examining tobacco smoking habits of patients with psychotic disorders is important since it is a major preventable risk factor for cardiometabolic disease – an important cause of premature death among people with schizophrenia (15). For adolescents, tobacco smoking might be an independent risk factor for developing psychotic disorders (7). However, it is still unclear to what extent tobacco smoking among high-risk patients is associated with increased risk for first psychotic episode, or could ceasing tobacco smoking prevent the onset of psychotic disorder among them, since to this date causality has not been proven (27).

In our sample, the percentage of the risk-level alcohol use, defined as AUDIT score ≥8 points, varied between 32.7% in the GPC group and 40% in the CHR-N group. There was no statistically significant difference between any clinical group compared to the GPC group. Participants from the FEP and CHR-N groups were more likely to consume 10 or more units of alcohol during one session, even though the frequency of binge drinking was not higher among them compared to the GPC group. Nevertheless, the percentage of the AUDIT-positive participants in our FEP group (38.1%) was equivalent to a previous study with Finnish schizophrenia patients (38.9%)(26). In this study, 22.1% of schizophrenia patients had a diagnosis for an alcohol use disorder; however, in this sample the percentage was higher among bipolar patients. These findings highlight that hazardous alcohol use is a common comorbidity among psychiatric patients in general, not exclusively among patients with psychotic disorders.

Among the participants presenting with FEP in this study, prevalence of cannabis use during lifetime (61.5%) and past 12 months (37.1%) was consistent with findings from previous studies (2,3) and significantly higher than in the GPC group (44.5% and 20.2%, respectively). Of note, among FEP patients, as many as one out of ten reported cannabis use 50 times or more during the past 12 months. In previous studies, especially heavy cannabis use has been associated with increased risk for developing schizophrenia (28). In another Finnish study, lifetime prevalence of cannabis use among FEP patients was found to be slightly lower (26%) (16). In that study cannabis use was evaluated with the combination of self-report questionnaire, clinical assessment and medical records. In a study with Finnish schizophrenia patients, prevalence of harmful use or dependence of cannabis was even lower (10.9%). However, in that study information of cannabis use was collected retrospectively from medical files suggesting that under-reporting might be an issue with the data (29). Moreover, cannabis use might be more prevalent among FEP patients compared to those with chronic schizophrenia, as cannabis use has been found to be more common among young patients (30). In our study, prevalence of cannabis use among other patient groups was similar to the GPC group. This finding might reflect the fact that cannabis use is widespread among the general population (31). However, a meta-analysis focusing on the association of cannabis abuse or dependence and onset of psychosis specifically in CHR populations reported a significant positive finding (6). Notably, a corresponding association between lifetime cannabis use and subsequent psychosis was not seen, which suggests a dose-response relationship. Also, a large birth cohort study has suggested rising substance use, especially cannabis, to be associated with higher prevalence of psychotic disorders (32). These findings highlight that even though cannabis use was not more common among CHR patients when compared to the

GPC group, and causality is still in debate, it is important to consider the frequency of use when treating this patient group.

In our study, prevalence of other illicit drug use was significantly more common in all patient groups compared to the general population controls. However, the prevalence of other illicit drug use was small, and power issues thus precluded from analysing different illicit drugs separately in the logistic regression models. In line with our result, a study with Finnish schizophrenia patients revealed relatively high lifetime prevalence of amphetamine (8.9%) and opioid (4.1%) abuse, both based on medical files (29).

The reason why substance use among people with psychotic disorders is markedly prevalent is not fully understood. FEP patients with comorbid substance use are typically described being male (33,34) and less educated than non-using patients (5). Male sex and low education have been associated with substance use in general population as well (35). Self-reported reasons for substance use among FEP patients include self-medication and facilitation of social interaction (36,37). Moreover, evidence from Mendelian randomization studies indicates shared genetic vulnerability for substance use and psychotic illnesses (38)

STRENGTHS AND LIMITATIONS

Strengths of this study include investigating use of several different substances, i.e. cigarette smoking, alcohol and wide variety of illicit drugs, within both first-episode and clinical high-risk patients. In addition, alcohol use was evaluated comprehensively with several variables. Importantly, psychosis status of the participants was assessed comprehensively using validated instruments, including the SCID-I and SIPS/SOPS interviews.

Some limitations need to be considered. In our study substance use was assessed by self-reports, and thus under-reporting might be a concern with our data (39). Also, the total number of participants wasn't significantly large, so power issues precluded from studying other illicit drugs than cannabis separately in the regression models. Our study did not consider polysubstance use either, which is known to be a common phenomenon (40). In addition, it needs to be considered that our data was collected from 2011 to 2017, and in the Finnish population there have been changes in the realm of substance use. The use of illicit drugs, especially cannabis, has become more common whereas the use of alcohol and smoking tobacco has decreased (41). Also, the study is cross-sectional in design and does not allow studying causality. Lastly, as this study was accomplished in the hospital district of South West Finland, results might not be generalizable to some other geographical or cultural contexts.

CONCLUSIONS

Our study provides new data on substance use among patients at clinical high risk for psychosis, an area with limited prior research. Our findings also align with earlier reports of high substance use in first-episode psychosis (FEP) in particular.

Our results highlight the importance of awareness and routine evaluation of substance use, not only among FEP but also psychosis-risk patients as a part of early interventions. Education of personnel is important for raising awareness on this topic. In clinical work, substance use can be evaluated with systematic interview, questionnaires and, if necessary, laboratory samples. Also, the opportunity to offer integrated substance use interventions for these patients would most likely have a favourable impact on their treatment outcomes.

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Formal analysis: LT, SN, JH
Investigation: JH, HL, TF, RKRS
Resources: JH, HL, TF, RKRS
Data management: LT, TF
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Declaration of interests

SN reports receiving personal fees from Camurus, dne Pharma, Lundbeck, Navamedic, Otsuka, Recordati and Takeda, all outside of this work.

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HAVE SCHIZOPHRENIA SPECTRUM DISORDERS AMONG CHILDREN AND ADOLESCENTS INCREASED IN THE 2010s

ABSTRACT

Background: *The demand for child and adolescent mental health services and psychiatric care has increased significantly in Western countries during the 21st century. Schizophrenia spectrum disorders and schizophrenia itself are rare but severe conditions, and their incidence has been assumed to rise alongside the increase in general psychiatric symptoms.* ***Objective:*** *Our aim was to examine the absolute numbers and incidence proportions of schizophrenia spectrum disorders and schizophrenia during the 2010s and to compare the findings with those from previous decades, among children and adolescents in contact with specialist level psychiatric services.* ***Materials and Methods:*** *The study population consisted of all under 18-year-old patients who had contact with specialized psychiatric services between 2010 and 2019. They were identified from the Finnish Care Register for Health Care (HILMO), and psychiatric primary diagnoses were based on the ICD-10 classification. To compare changes across earlier decades, data from adolescents with their first inpatient contact in specialized psychiatric care between 1980 and 2009 were utilized. Statistical analyses included chi-square tests to assess differences between groups and Cox proportional hazards regression models to estimate risk.* ***Results:*** *The disorders were rare, and neither the number of diagnosed cases nor the risk of developing the disorder changed during the 2010s. The number of patients with schizophrenia spectrum diagnoses admitted for their first psychiatric inpatient treatment decreased compared to the previous decade, and the number of schizophrenia diagnoses has declined steadily since the 1980s. However, the absolute number of schizophrenia spectrum disorders stabilized at a higher level in the 2000s compared to earlier decades.* ***Conclusions:*** *Schizophrenia spectrum disorders have not increased among children and adolescents during 2010s. The variation in the number of schizophrenia spectrum disorders across decades with eventual stabilization at a higher level is likely due to changes in diagnostic practices. However, these severe disorders appear to be less influenced by broader societal changes than other disorders.*

KEYWORDS: PSYCHOSES, SCHIZOPHRENIA, CHILD AND ADOLESCENT PSYCHIATRY, REGISTER STUDY, SECULAR TRENDS

INTRODUCTION

The demand for child and adolescent mental health services and psychiatric care has increased in Western countries during the 21st century (1,2,3), to the extent that it has been described as a mental health crisis. In particular, anxiety and depressive symptoms among children and adolescents have become more prominent, and the use of psychiatric services has increased especially among adolescent girls (2,3).

Schizophrenia spectrum psychoses are severe mental disorders characterized by symptoms typically divided into positive and negative categories. Positive symptoms include hallucinations, delusions and disorganized behaviour, whereas negative symptoms include diminished emotional expression and social withdrawal (4,5). Schizophrenia most commonly manifests in adolescence or early adulthood. On average, onset occurs approximately five years earlier in males than in females (6,7). The onset is usually preceded by a prodromal phase, during which individuals experience non-specific symptoms such as anxiety and depression, as well as mild psychotic symptoms, including perceptual disturbances (5,7). Previous studies suggest that the incidence of schizophrenia in adults has increased globally over recent decades. This increase has been attributed to advances in scientific knowledge and

improvements in clinical recognition. In addition, it has been proposed that the improved identification of other psychiatric disorders and the associated increase in help-seeking behaviour have contributed, and will continue to contribute, to the rising number of schizophrenia diagnoses (8,9,10). An increase in the incidence of schizophrenia among children and adolescents has also been suggested, although this age group has been studied less extensively (8).

Only a very small proportion of schizophrenia spectrum psychoses emerge in childhood. In very early-onset schizophrenia (VEOS), the disorder manifests before the age of 13, with an estimated incidence of less than 0.04% (11,12). Early-onset schizophrenia (EOS) is defined as onset between the ages of 13 and 18. The incidence of schizophrenia increases significantly after the age of 15 (7,12,13). Both VEOS and EOS are severe disorders, characterized not only by core schizophrenia symptoms but also by substantial neurocognitive impairments (13).

Diagnosing schizophrenia during developmental years is particularly challenging, as children and adolescents are still undergoing maturation and comorbid psychiatric disorders are common, especially in association with schizophrenia. Symptoms of different disorders often overlap (11,12). Fewer than 10% of all schizophrenia diagnoses are made before the age of 18 (14). Although schizophrenia typically has an earlier onset in males, females tend to access psychiatric care approximately one year earlier than males. This has been attributed to clearer symptom presentation and better recognition in females (15).

It remains unclear to what extent the observed increase in mental health problems among children and adolescents and the rising demand for treatment (1,2,3) reflect a true increase in morbidity, and to what extent they may be explained by the medicalization of normal developmental challenges or by changes in environmental demands that increase the need for support in the presence of psychiatric symptoms (16,17). The expansion of treatment options and increased awareness have also contributed to higher service utilization (18). The growing demand for care among adolescents is particularly associated with depressive and anxiety disorders, while in children it is more often linked to behavioural symptoms such as ADHD. The need for care related to psychotic disorders might be expected to be less sensitive to societal discourse than that related to milder disorders. On the other hand, the incidence of schizophrenia spectrum psychoses during developmental age could increase if non-specific symptoms—potentially representing prodromal manifestations—more frequently lead to treatment contact and earlier diagnosis of psychotic disorders.

Since the late 1970s, a comprehensive, age-specific system of child and adolescent psychiatric services has been established in Finland (19). A Finnish register-based study examined the incidence and treatment of mental disorders among adolescents from the 1980s to 2010. The number of individuals diagnosed with schizophrenia at the time of first contact remained consistently low. The risk of receiving a later schizophrenia diagnosis among those initially treated for other disorders decreased from the 1980s to the 2000s (19). This may be attributable to improved diagnostic accuracy and earlier access to treatment during the 2000–2010 period, potentially reducing the risk of progression to psychotic disorders. Subsequent diagnostic conversion to schizophrenia occurred particularly among individuals with other schizophrenia spectrum disorders and severe mood disorders (19).

The Finnish Care Register for Health Care (HILMO) contains nationwide data on the use of health services, access to care, epidemics and other health-related issues (20). HILMO data are used for the compilation of national and international statistics, research and service planning (21). It is a comprehensive and reliable nationwide reporting system covering inpatient care in hospitals and health centres, as well as outpatient specialized care in the public sector (21). Given the severity of schizophrenia spectrum psychotic disorders, it is reasonable to assume that affected patients eventually receive care in specialized services, supporting the epidemiological representativeness of HILMO data for these conditions.

The aim of this study is to examine whether the number of children and adolescents diagnosed with schizophrenia or, more broadly, schizophrenia spectrum disorders has increased in Finland during the 2010s, in the context of heightened societal attention to mental health problems in developmental age and increased referrals to specialized psychiatric care. In addition, the incidence of schizophrenia spectrum disorders and schizophrenia is analysed according to developmental stage, sex and the disorders leading to initial treatment contact. Among adolescents admitted for their first inpatient psychiatric treatment, the incidence of schizophrenia spectrum disorders and schizophrenia is compared with corresponding figures from previous decades.

MATERIALS AND METHODS

The study population consisted of all individuals under 18 years of age who had contact with specialized psychiatric services between 2010 and 2019. They were identified from the Finnish Care Register for Health Care (HILMO). In this study,

the following information was used from all their psychiatric treatment episodes in specialized care: dates of admission and discharge up to the end of 2021, primary psychiatric diagnosis according to the ICD-10 classification, age at the time of contact and sex.

Psychiatric diagnoses were analysed at the level of the main ICD-10 categories of mental and behavioural disorders (F00–F09, F10–F19, etc.), with the exception of schizophrenia spectrum disorders. These were examined both as a whole (F20–F29) and separately, with a focus on schizophrenia and schizoaffective disorder (F20 + F25), which together form an extended definition of schizophrenia (22).

To assess potential changes compared with previous decades, the data were compared with a register-based cohort of individuals aged 13–17 years who were admitted to their first adolescent psychiatric inpatient episode between 1980 and 2009. This comparison dataset has been described previously (19,23,24). For this analysis, the current dataset was restricted using the same criteria to include adolescents aged 13–17 years who were admitted to their first psychiatric inpatient episode between 2010 and 2019.

STATISTICAL ANALYSES

The incidence of schizophrenia spectrum disorders and schizophrenia was examined by sex, age group and primary diagnosis at first contact using cross-tabulation. We explored the absolute numbers of emerging cases and incidence proportions as the number of new cases divided by the number of all patients, rather than by person-years of follow-up. Statistical significance was assessed using the chi-square test. The risk of receiving a diagnosis of schizophrenia spectrum disorder or schizophrenia was examined using multivariable Cox proportional hazards regression models, which account for differences in follow-up time among patients entering the study in different years. The outcomes were defined as: 1) a diagnosis within the F20-29 category and 2) an extended schizophrenia diagnosis. The explanatory variables included year of first contact, age group, sex and primary diagnosis at first contact. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported.

Among adolescents aged 13–17 years admitted for their first psychiatric inpatient treatment, the following were examined: 1) the absolute number of F20-29 diagnoses and 2) the number of extended schizophrenia diagnoses during the first treatment episode over the decade, and these were compared with corresponding figures from the 1980s, 1990s and 2000s. In annual analyses for the 2010s, cross-tabulations were used to examine trends in the number of first inpatient treatment episodes with an F20-29 primary diagnosis, as well as the total number of inpatient episodes associated with F20-29 diagnoses and with F20/F25 diagnoses.

Due to the large sample size and multiple testing, statistical significance was set at $p<0.01$.

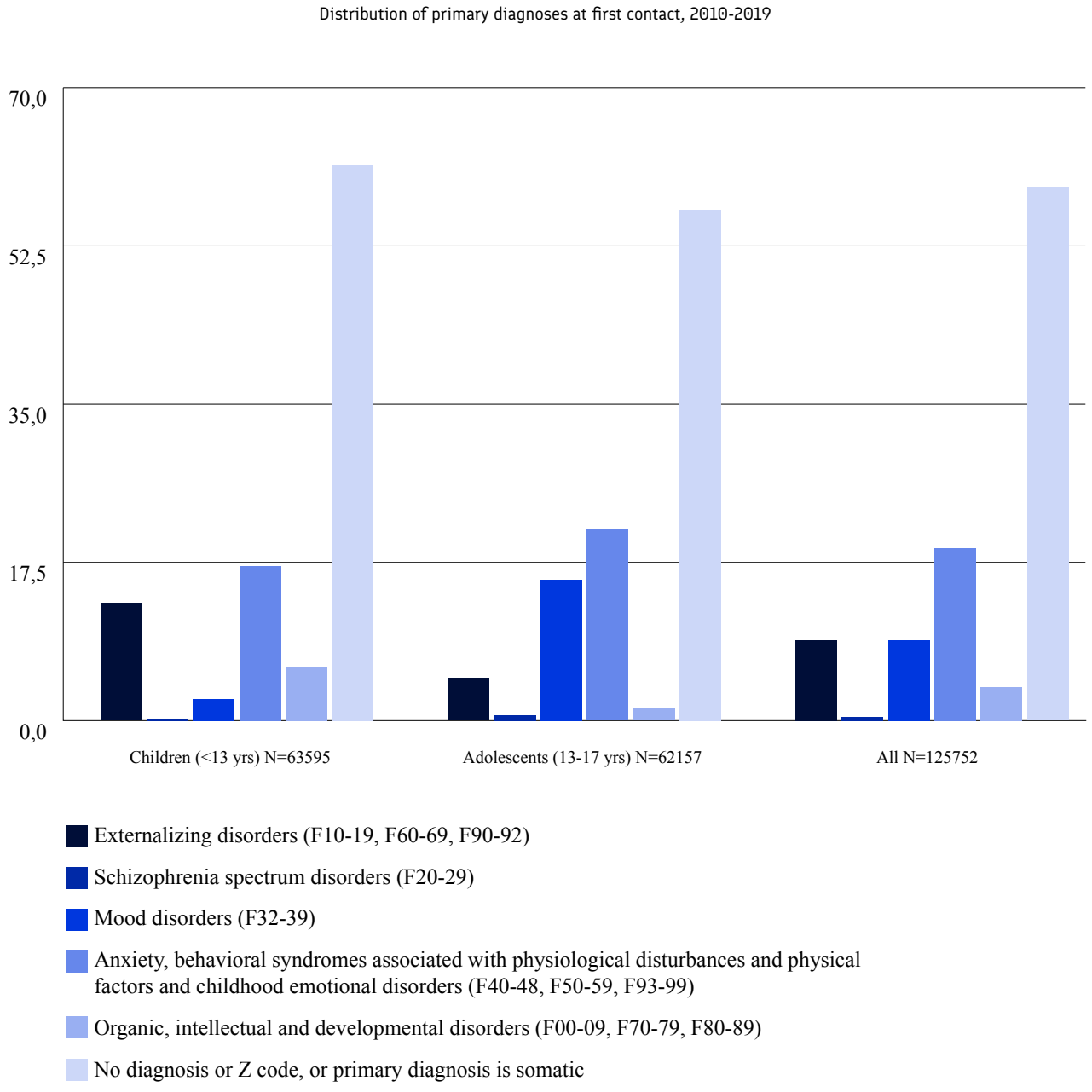
RESULTS

CHILDREN AND ADOLESCENTS AT FIRST CONTACT

The dataset included all children and adolescents who had their first contact with specialized psychiatric services (outpatient and inpatient care) between 2010 and 2019. Among these contacts, 62,157 were adolescents (aged 13–17 years), of whom 68.8% (n=42,764) were female and 31.2% (n=19,393) were male. The number of children (under 13 years of age) at first contact was 63,595, of whom 62.2% (n=39,556) were male and 37.8% (n=24,039) were female. Thus, the sex distribution among children was the reverse of that observed among adolescents.

Figure 1 presents the distribution of primary diagnoses assigned at first contact among children and adolescents in specialized psychiatric care between 2010 and 2019. Overall, 59.0% of individuals did not receive a psychiatric primary diagnosis at first contact.

Figure 1. Distribution of primary diagnoses among children and adolescents at first contact with specialized psychiatric care



SCHIZOPHRENIA SPECTRUM DIAGNOSES AND SCHIZOPHRENIA AMONG PATIENTS IN CHILD AND ADOLESCENT PSYCHIATRIC SERVICES IN THE 2010s

Among adolescents, 1.5% (n=403) received a schizophrenia spectrum diagnosis (F20–F29) at first contact. Among children, the corresponding proportion receiving an F20-29 diagnosis was 0.2% (n=43). A diagnosis of schizophrenia (F20/F25) at first contact was assigned to eight adolescents. No child received a schizophrenia diagnosis at first contact. During the follow-up period, 3.0% (n=3,802) of all individuals who had first contact received an F20-29 diagnosis. Among those who first presented in adolescence, the proportion was 4.9% (n=3,054), and among those who first presented in childhood, 1.2% (n=748). A schizophrenia diagnosis during follow-up was assigned to 0.7% (n=922) of all patients: 1.3% (n=820) among those first presenting in adolescence and 0.2% (n=102) among those first presenting in childhood.

Tables 1 and 2 present the incidence of F20-29 diagnoses among children and adolescents, and the incidence of F20/F25 diagnoses among adolescents, according to diagnoses at first contact.

Among individuals who first entered treatment in childhood, an F20-29 diagnosis during follow-up was most commonly assigned to those who had a mood disorder (F30–F39) at first contact. Among those first treated in adolescence, F20-29 diagnoses occurred most frequently in individuals whose initial diagnosis belonged to the category F00–F09, F70–F79 or F80–F89 (*Table 1*). Among adolescents at first contact with specialized psychiatric services, a schizophrenia diagnosis during follow-up was most commonly assigned to those who had already received another F20-29 diagnosis at first contact. Among those with other initial diagnoses, conversion to a schizophrenia spectrum disorder occurred in 1.2–1.5% of cases (*Table 2*). Due to the low number of cases, a corresponding analysis could not be conducted among those first treated in childhood.

MULTIVARIABLE ANALYSES

In the multivariable models, the risk of receiving any F20-29 diagnosis or, more specifically, a diagnosis of F20/F25 did not change over the course of the decade (*Tables 3 and 4*). No statistically significant time-dependent association was observed in the analysis (F20-29: HR=1.0, p=0.15; F20/25: HR=1.0, p=0.12). Compared with females, males had a 1.6-fold higher risk of receiving an F20-29 diagnosis and a 2.1-fold higher risk of receiving an F20/F25 diagnosis. Individuals whose first contact occurred during adolescence had a 4.6-fold higher risk of an F20-29 diagnosis and a 9.4-fold higher risk of an F20/F25 diagnosis compared with those whose first contact occurred in childhood. Compared with individuals who did not receive a psychiatric diagnosis at first contact, the risk of a subsequent F20-29 diagnosis was increased across nearly all diagnostic categories, with the exception of the group "Organic, intellectual, and developmental disorders" (F00–F09, F70–F79, F80–F89). Having a non-F20/F25 diagnosis within the F20-29 category at first contact strongly predicted a later schizophrenia diagnosis, with a 14.6-fold increased risk (*Tables 3 and 4*).

ADOLESCENTS AGED 13–17 AT FIRST INPATIENT ADMISSION: COMPARISON WITH PREVIOUS DECADES

The dataset included 15,020 adolescents whose first psychiatric inpatient episode occurred between the ages of 13 and 17 during the years 2010–2019. Of these, 69.7% (n=10,437) were female and 30.3% (n=4,547) were male. Among the adolescents, 37.4% were in early adolescence (13–14 years) and 62.6% in middle adolescence (15–17 years). *Table 5* presents the number of adolescents who received an F20-29 diagnosis or an F20/F25 diagnosis as the primary diagnosis during their first inpatient treatment episode between 2010 and 2019, compared with corresponding figures from previous decades. The number of individuals receiving a schizophrenia spectrum diagnosis at their first psychiatric inpatient episode has fluctuated across decades but has stabilized at a higher level in the 2000s compared to earlier decades, whereas the number of those receiving a schizophrenia diagnosis has decreased (*Table 5*).

Figure 2 shows the annual number of first inpatient treatment episodes with an F20-29 primary diagnosis, as well as the total number of inpatient episodes with F20-29 and F20/F25 primary diagnoses among adolescents during the 2010s. The relative proportions of both first inpatient episodes and all inpatient episodes with an F20-29 diagnosis decreased over the decade (Mantel–Haenszel test $p<0.001$ for both), as did the proportion of all inpatient episodes with an F20/F25 diagnosis ($p<0.001$). A modest decrease in absolute numbers is also observed in the curves representing the entire F20-29 category (*Figure 2*). First inpatient episodes with an F20/F25 diagnosis are not presented annually due to the low number of cases.

Table 1. Proportion of individuals who subsequently received an F20-29 diagnosis during follow-up among individuals with first contact in childhood and adolescence, according to diagnosis at first contact

Initial diagnosis	Children	Adolescents	p[1]
Externalizing disorders (F10-19, F60-69, F90-92)	1.1%	5.6%	<0.001
Mood disorders (F30-39)	3.1%	5.2%	<0.001
Anxiety, behavioural syndromes associated with physiological disturbances and physical factors and childhood emotional disorders (F40-48, F50-59, F39-99)	1.3%	4.7%	<0.001
Organic, intellectual and developmental disorders (F00-09, F70-79, F80-89)	0.9%	6.7%	<0.001
No psychiatric diagnosis	1.0%	3.7%	<0.001

[1] comparison between age groups

Table 2. Proportion of individuals who subsequently received an F20/25 diagnosis during follow-up among individuals with first contact in adolescence, according to diagnosis at first contact

Initial diagnosis	
Externalizing disorders (F10-19, F60-69, F90-92)	1.5%
Schizophrenia spectrum disorders (F20-29 excl. F25/F20)	22.8%
Mood disorders (F30-39)	1.4%
Anxiety, behavioural syndromes associated with physiological disturbances and physical factors and childhood emotional disorders (F40-48, F50-59, F39-99)	1.2%
Organic, intellectual and developmental disorders (F00-09, F70-79, F80-89)	1.5%
No psychiatric diagnosis	1.0%

Table 3. Hazard ratios with confidence intervals for schizophrenia spectrum (F20-29) diagnosis (hazard ratio [HR], 95% confidence interval [CI]) during follow-up among minors in specialized psychiatric care in the 2010s, according to sex, age, diagnosis at first contact and year of first contact

	HR (95% confidence interval)	p
Sex		
Female	reference	
Male	1.6 (1.5–1.7)	<0.001
Age group at first contact		
Child (<13 years)	reference	
Adolescent (13–17 years)	4.6 (4.2–5.1)	<0.001
Year of first contact (continuous variable)	1.0 (1.0–1.0)	0.15
Diagnosis at first contact		
No psychiatric diagnosis	reference	
Externalizing disorders (F10-19, F60-69, F90-92)	1.2 (1.1–1.4)	0.006
Mood disorders (F30-39)	1.4 (1.3–1.5)	<0.001
Anxiety, behavioural syndromes associated with physiological disturbances and physical factors and childhood emotional disorders (F40-48, F50-59, F39-99)	1.3 (1.2–1.4)	<0.001
Organic, intellectual and development disorders (F00-09, F70-79, F80-89)	1.2 (1.0–1.5)	0.11

Table 4. Hazard ratios with confidence intervals for schizophrenia (F20/F25) diagnosis (hazard ratio [HR], 95% confidence interval [CI]) during follow-up among minors in specialized psychiatric care in the 2010s, according to sex, age, diagnosis at first contact and year of first contact

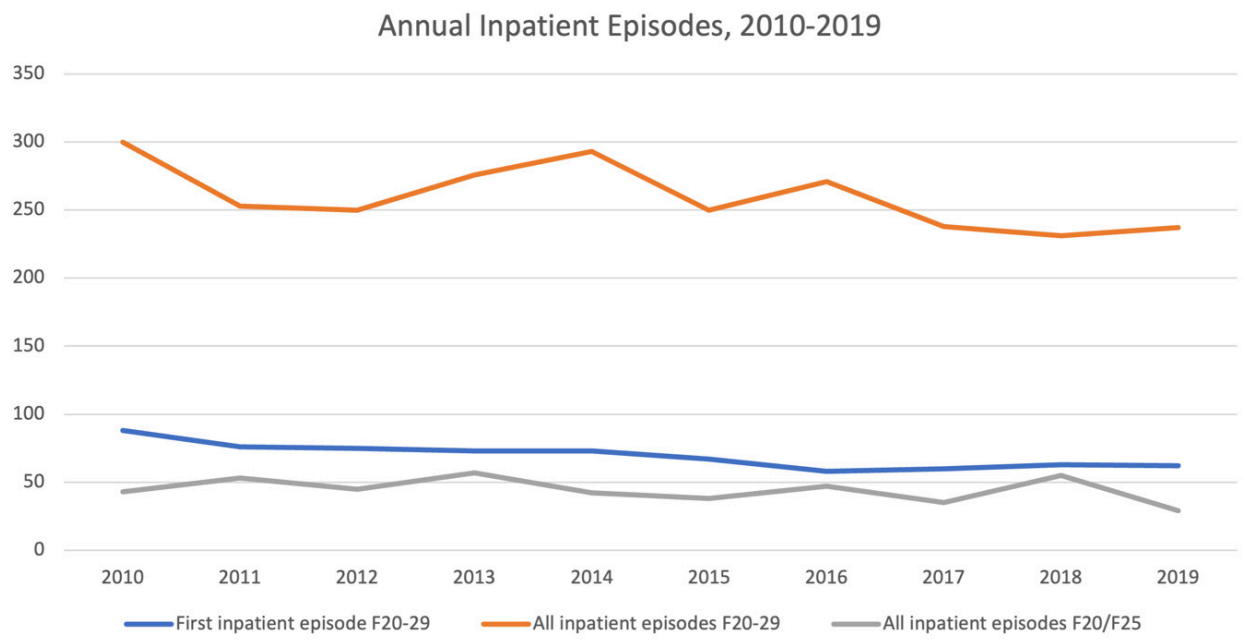
	HR (95% confidence interval)	p
Sex		
Female	reference	
Male	2.1 (1.8–2.4)	<0.001
Age group at first contact		
Child (<13 years)	reference	
Adolescent (13–17 years)	9.4 (7.6–11.7)	<0.001
Year of first contact (continuous variable)	1.0 (1.0–1.1)	0.12
Diagnosis at first contact		
No psychiatric diagnosis	reference	
Externalizing disorders (F10-19, F60-69, F90-92)	1.2 (0.9–1.5)	0.2
Schizophrenia spectrum disorders (F20-29, excl. F25/F20)	14.6 (11.6–18.3)	<0.001
Mood disorders (F30-39)	1.3 (1.1–1.6)	0.003
Anxiety, behavioural syndromes associated with physiological disturbances and physical factors and childhood emotional disorders (F40-48, F50-59, F39-99)	1.2 (1.0–1.4)	0.044
Organic, intellectual and developmental disorders (F00-09, F70-79, F80-89)	0.9 (0.5–1.4)	0.57

Table 5. Number of individuals receiving an F20–29 diagnosis and an F20/F25 diagnosis as the primary diagnosis at their first inpatient episode between 2010 and 2019, compared with corresponding figures reported for previous decades (Holttinen 2023)

	1980–1989 *	1990–1999*	2000–2009*	2010–2019
F20–29				
All	569	474	800	695
Boys	280	235	388	352
Girls	289	239	412	343
F20/25				
All	192	41	75	26
Boys	92	20	30	14
Girls	100	21	45	12

* Holttinen T. Finnish Adolescents Treated in Psychiatric Inpatient Care from 1980 to 2010 and Their Long-term Life Situations, 2023

Figure 2. Annual number of initial inpatient episodes and all inpatient episodes among adolescents with F20–29 group diagnoses, and all inpatient episodes with F20/F25 diagnoses



DISCUSSION

This register-based study examined the absolute numbers and incidence proportions of schizophrenia spectrum disorders and schizophrenia among children and adolescents during the past decade. Among all children and adolescents who had contact with specialized psychiatric services, both schizophrenia spectrum disorders and schizophrenia were rare, and the number of individuals receiving these diagnoses remained stable throughout the 2010s. Among adolescents aged 13–17 years admitted for their first psychiatric inpatient episode, comparison with corresponding data from previous decades (19) suggested a decrease in schizophrenia spectrum diagnoses compared to the previous decade and a decline in schizophrenia diagnoses since the 1980s.

Referrals of children and adolescents to specialized psychiatric services have been increasing for a prolonged period (19,25). Awareness of mental health disorders has improved, leading an increasing number of individuals to seek care (26). This has also been suggested to potentially increase the number of diagnosed schizophrenia spectrum disorders (8,9,10). However, the widely recognized mental health crisis among children and adolescents does not appear, based on this study, to be reflected in the number of schizophrenia spectrum disorder diagnoses. These disorders are inherently severe and may be less sensitive to environmental factors and societal trends than conditions such as depressive and anxiety disorders.

Among adolescents aged 13–17 years admitted for their first inpatient episode, comparisons across decades were possible (19). The absolute number of schizophrenia spectrum disorder diagnoses has varied across decades but has stabilized at a higher level since the 2000s compared to earlier periods. This may reflect improved recognition of these disorders. The observed variation across decades, as well as the particularly high numbers in the 2000s, may be explained by evolving diagnostic practices over time. This variability could be reduced through the systematic use of structured diagnostic methods. Alternatively, it is also possible that the true incidence of schizophrenia spectrum disorders among adolescents has increased since the 1980s. Substance use, particularly cannabis use, has been shown to contribute to and accelerate the onset of schizophrenia (27). In Finland, cannabis use among adolescents increased up until the 2010s and has remained relatively stable thereafter (28). The consistent decline in diagnoses of schizophrenia itself since the 1980s is most likely a result of more refined diagnostic

processes. Previous research does not allow for a similar long-term comparison of these diagnoses among children in Finland.

The incidence of schizophrenia spectrum disorders and schizophrenia was markedly higher among adolescents at their first contact with specialized psychiatric services compared to those who required specialized care already during childhood. Psychiatric symptoms requiring specialized care in childhood are more likely to be associated with environmental factors and living conditions and may be more modifiable, whereas disorders emerging in adolescence are more strongly linked to genetically influenced psychiatric processes that play a greater role in the need for treatment. Most psychiatric disorders begin during adolescence and frequently co-occur (29,30). Among children under 13 years of age, schizophrenia spectrum disorders are considerably rarer than in adolescence (31,32).

Boys in our dataset had a higher risk of developing schizophrenia spectrum disorders compared with girls. This finding is consistent with previous evidence indicating that schizophrenia is more common in males than in females (33) and has an earlier onset in males (6,7). Since the majority of the study population had reached at most young adulthood by the end of follow-up, the prevalence of schizophrenia spectrum disorders in this cohort can be expected to increase further over time. Previous research on sex differences in schizophrenia has mainly focused on the general population rather than specifically on children and adolescents.

The risk of developing a schizophrenia spectrum disorder was relatively similar regardless of the initial diagnostic classification assigned at first contact, and the risk of developing schizophrenia itself was likewise comparable across most diagnostic groups, with the exception of those already diagnosed with an F20-29 disorder at first contact, for whom the risk was markedly elevated. Prodromal symptoms in children and adolescents are typically non-specific, and comorbidity with other psychiatric disorders is common in psychotic disorders (11,12,30). Prodromal symptoms may be difficult to recognize as such before the emergence of overt psychotic symptoms. Furthermore, during developmental stages, non-specific and transient psychotic symptoms are more common than in adults and do not necessarily indicate an F20-29 spectrum psychotic disorder (34). On the other hand, the process of establishing a diagnosis may be delayed in these age groups due to the requirement for thorough assessment and prolonged follow-up (35). Among children, conversion to an F20-29 diagnosis occurred most frequently in those initially diagnosed with mood disorders (F30–F39), whereas among adolescents, conversion was slightly more common in those with organic, intellectual and developmental disorders (F00–F09, F70–F79, F80–F89). Severe mood disorders may represent prodromal manifestations, whereas genetically determined conditions within the F00–F09, F70–F79 and F80–F89 categories may reflect underlying structural vulnerability (36,37). The strongest predictor of later schizophrenia was a prior non-F20/F25 diagnosis within the F20-29 category. Schizophrenia is thought to develop in stages, and studies suggest that a substantial proportion—up to 36%—of other psychotic disorders eventually convert to schizophrenia (38). In contrast, progression to a schizophrenia diagnosis from other initial diagnostic categories was considerably less common.

METHODOLOGICAL CONSIDERATIONS

The dataset comprised all minors who had contact with specialized psychiatric services during the study decade. National register data are extensive and comprehensive and are not affected by attrition, as service providers are obliged to report data to the register in a standardized manner. Because the dataset includes all children and adolescents who accessed specialized psychiatric care, it is not subject to selection bias. Register-based data are particularly suitable for the analysis of psychotic disorders, as the validity of psychosis diagnoses in Finnish registers has been shown to be high (39,40). Furthermore, individuals with these disorders are less likely to participate in surveys and interviews (9). The Finnish Care Register for Health Care (HILMO), from which the patient data were obtained, is a reliable and standardized database, and the use of ICD-10 diagnoses ensures consistency across classifications. Register-based data are particularly valuable for studying incidence and causal relationships (41,42).

However, register-based data also have limitations. Diagnostic practices may vary between clinicians and across regions. It is also possible that some patients received another psychiatric diagnosis or a schizophrenia spectrum diagnosis (F20–F29 excluding F20/F25) instead of a diagnosis of schizophrenia (F20/F25). This naturally affects the number of cases in both diagnostic groups. In particular, clinicians may exercise caution when diagnosing schizophrenia during developmental years, which may delay the assignment of this diagnosis (43). Nevertheless, schizophrenia spectrum diagnoses made in adolescence have been shown to be highly stable over time (24).

A considerable share of children and adolescents did not receive a formal diagnosis at their first visit to specialist level psychiatric care. In such cases most likely a formal diagnosis will follow in due time. An option would have been to use the first recorded psychiatric diagnosis. However, we wanted to

treat all cases systematically in the same way and therefore categorized diagnoses at first contact including the no/Z group. Further, obviously no formal psychiatric diagnosis at first contact finally was meaningful, indicating milder disturbance (and may be rather social problems), as almost all other categories deviated from it in prognosis.

Our comparison over decades focused on numbers of adolescents admitted to their first ever psychiatric inpatient care due to F20-29 and due to schizophrenia. While this cannot be considered actual epidemiological exploration of incidence in the adolescent population, these numbers likely represent total new onset cases very well, since adolescents with first episodes of these disorders most likely come to psychiatric care and are also admitted to inpatient treatment. In this analysis we did not report developments in proportion of those with these diagnoses of all patients admitted, because vast increases in admissions due to internalizing disorders over the decades (Niemi et al. 2023) would then create a biased impression that F20-29 diagnoses had decreased.

CONCLUSIONS

Among children and adolescents who had contact with psychiatric services, the likelihood of receiving a diagnosis of a schizophrenia spectrum disorder or schizophrenia did not increase during the 2010s. This finding most likely reflects the situation in the general population, as the severity of these disorders makes it highly likely that affected individuals will come into contact with specialized care. Among adolescents admitted for their first psychiatric inpatient episode, schizophrenia spectrum diagnoses have been more common in the 2000s than in earlier decades, but their frequency decreased in the 2010s compared to the previous decade. Diagnoses of schizophrenia itself have declined since the 1980s. This likely reflects improved diagnostic precision. It is also possible that earlier and more effective treatment has prevented or delayed the onset of schizophrenia as a full-blown disorder until adulthood. Even if schizophrenia is diagnosed later, a delayed onset allows for better development of functioning during adolescence, which is beneficial in itself. Further research is needed to clarify the impact of evolving diagnostic practices, early identification of psychosis and their role in guiding interventions on long-term outcomes and functional capacity among children and adolescents with psychiatric disorders.

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DOES MORE PSYCHIATRIC INPATIENT TREATMENT DURING ADOLESCENCE PREDICT MORE OR LESS INPATIENT TREATMENT IN ADULTHOOD? A REGISTER BASED 10-YEAR FOLLOW-UP STUDY

ABSTRACT

Previous research has produced inconsistent findings regarding whether the amount of inpatient care during adolescence predicts later treatment needs in adulthood. The aim of this study was to examine whether the extent of adolescent psychiatric inpatient care is associated with recurrent hospitalization and the accumulation of inpatient days in adulthood, and whether these associations are independent of age, sex, diagnosis and decade of first admission. This nationwide register-based cohort study included all adolescents aged 13–17 who were admitted to psychiatric inpatient care for the first time between 1980 and 2010 (n=16 842). Adolescent inpatient days were calculated from all hospitalizations occurring before age 18, and adult inpatient days from hospitalizations during a ten-year follow-up period (ages 18–27). Associations were first analysed using cross-tabulations, and multivariable logistic regression models were used to account for potential confounders. A greater number of adolescent inpatient days was associated with a higher likelihood of readmission and a larger number of inpatient days in adulthood. Older age at first admission, diagnostic group and earlier decade of admission also predicted the occurrence and amount of inpatient care during follow-up. Among individuals with schizophrenia spectrum disorders, the association between adolescent inpatient days and adult inpatient care was not as pronounced as in other diagnostic groups; instead, the need for care remained relatively stable regardless of the amount of adolescent hospitalization, likely reflecting the nature of the disorder. These findings highlight the importance of strengthening outpatient services and supporting symptom management and functional capacity in adolescents within their natural developmental environments.

KEYWORDS: ADOLESCENT PSYCHIATRY, INPATIENT CARE, READMISSIONS, REGISTER STUDY

INTRODUCTION

Adolescence is a critical period for the onset of mental health disorders – most mental health disorders begin during adolescence or young adulthood, and many disorders that begin in adolescence continue into adulthood or reappear later in life (1–3). About one adolescent in five has a psychiatric disorder (4). Rapid changes in physical, cognitive, emotional and social development can contribute to the onset of mental health disorders during this sensitive period (5). There is an increase in rates of depression, panic disorder and substance use disorder (SUD) when moving from childhood to adolescence, as well as a decrease in ADHD and SAD (separation anxiety disorder)(4). Comorbidity, that is the simultaneous occurrence of multiple mental health disorders, is common in young people, as well as in adults.

Inpatient care could be considered most beneficial for those who have not received sufficiently effective treatment from lighter forms of psychiatric care, such as outpatient or day patient services, but there is only limited research evidence on which specific behavioural or symptom-related factors or criteria that would indicate the need for psychiatric inpatient treatment (6). In Finland, adolescent mental health treatment is more accessible compared to the European average (7). Adolescent psychiatric services in Finland are mainly provided by publicly funded specialist-level healthcare units, which commonly offer both inpatient and outpatient services in central hospitals. Additionally, student healthcare plays an important role in the

early detection of mental health disorders, treatment of mild and moderate disorders and referral to specialized treatment. Most adolescent psychiatric treatment and mental health services are provided on an outpatient basis.

In Finland, the first adolescent psychiatric ward was founded in Pitkäniemi, Nokia, in 1959, and shortly thereafter in Hesperia, Helsinki, in 1961 (8). In the Mental Health Act of 1991, it was emphasized that adolescent psychiatric inpatient care should take place in its own units, separate from adult psychiatric wards. At first, this led to a significant increase in the number of beds in adolescent psychiatric wards during the 1990s—up to 130% compared to previous levels—at the same time as the number of adult psychiatric ward beds decreased as a result of deinstitutionalization (9). In 1999, adolescent psychiatry became its own medical specialty, separated from both child and adult psychiatry. During the 2000s, adolescent psychiatric treatment increasingly shifted from ward-based to outpatient-based, and the length of inpatient stays shortened (10).

Inpatient care provides advantages over outpatient care by offering a safe, round-the-clock environment to manage serious symptoms such as suicidal behaviours, productive psychotic symptoms or severe eating disorder symptoms. It also enables close monitoring of medication response and provides structured support for reducing health-compromising behaviours such as substance use or passivity. Educational needs may be managed effectively in hospital school, and the ward community may provide peer support that is of utmost importance during adolescent years. Mental health challenges have been found to be associated with other health and developmental difficulties among young people, such as poorer academic performance, sexual health issues and increased substance use (2). Comorbid diseases such as diabetes and obesity, among other risk factors, reduce life expectancy of these patients by up to 10–20 years (12,13). Inpatient units can provide additional support to look after these habits and offer alternative activities and groups instead.

Inpatient care may in certain situations also take place on an involuntary basis. In Finland, criteria for adolescent psychiatric inpatient care are that the young person presents with a serious mental health disorder and is in need of treatment in a way that failure to submit to treatment would significantly endanger their health or safety or the health or safety of other people, and other mental health services are not suitable (Mental Health Act 1116/1990).

Inpatient treatment is not without downsides. Symptom contagion is a known risk in, for example, eating disorders and suicidal behaviours (14–16). Stigma related to mental disorders may be pronounced in inpatient care (17). During inpatient treatment, adolescents also miss out on the social interaction that young people generally engage in at school and in their hobbies. The patient's own leisure activities are put on hold during the treatment, which can affect coping, especially when the activity has previously been an important asset in their everyday life. Furthermore, the increase in autonomy that comes with adolescence is reduced while being an inpatient, as the inpatient care limits the young person's control over their actions and activities (11). After treatment, the transition back to normal life can be stressful if sufficient support is not available at that stage (18,19).

In conclusion, inpatient care can provide an opportunity for intensive treatment and individual support, but it can also cause unwanted changes in the patient's life and restrict their freedom in ways that outpatient or day care does not. Acute inpatient admissions mainly take place in situations where they are unavoidable. Long-term inpatient care can be more subject to debate. However, in subsequent crises, the threshold for inpatient admission may lower (20,21), and repeated inpatient admissions finally constitute considerable total time spent in inpatient care. The benefits and disadvantages of more inpatient treatment, as opposed to minimizing inpatient care, have not been studied widely enough to determine which provides better functioning in the long term. Some studies have yielded support for long hospital stays, suggesting they improve the patient's functional capacity more than a short stay, while other results support that the length of the hospital stay has no significance in functional capacity (11). Instead, recent research evidence indicates that a first psychiatric inpatient admission occurring in early adulthood predicts a continued need for long-term clinical psychiatric care (22).

In this study, we aim to survey the connections between time spent in inpatient psychiatric care during adolescence and rehospitalization during the 10-year follow-up among those who were admitted to hospital between ages 13 and 17 for the first time. Providing intensive care during developmental years in the form of inpatient treatment could result in improvements that permanently decrease the need for inpatient treatment in subsequent developmental stages. On the other hand, there may be a risk that both repeated admissions and lengthy stays become a helplessness-reinforcing solution to a multitude of challenges for the young person and their environment, as suggested in the labelling theory of mental illness (20). Therefore, we set out to answer the following questions:

1. Does the total time spent in hospital care during adolescence predict rehospitalization in adulthood?

2. Does the total time spent in psychiatric inpatient care during adolescence have predictive significance for time spent in inpatient care in ten-year follow-up after coming of age?
3. Are the possible longitudinal associations of time spent in inpatient care during adolescence with rehospitalization and time spent in inpatient care in 10-year follow-up independent of sex, age, diagnosis at first admission and decade of the first admission?

MATERIALS AND METHODS

The present study comprises a register-based naturalistic follow-up study of adolescent psychiatric inpatients. All the patients admitted to adolescent psychiatric inpatient care for the first time between 1980 and 2010 at ages 13-17 in Finland, diagnosed with psychiatric disorders (F diagnoses), Z codes or neurological disorders (G diagnoses) as per ICD-10, were identified from the National Care Register in Health Care (CRHC) database (n=16 842). The Finnish Care Register for Health Care (HILMO) has systematically recorded all episodes of specialized medical care in Finland since 1994. Its predecessor, the national hospital discharge register, encompassed all patients released from inpatient hospital care within Finnish health services between 1969 and 1993. The fundamental data elements and overall structure of these registers have remained largely stable throughout the entire study period. From these nationwide registers, data were extracted on patients' age, sex, psychiatric diagnoses, the dates marking the initiation and termination of inpatient treatment for each patient's first inpatient stay (=index admission) and dates of initiation and termination of all their subsequent psychiatric inpatient admissions.

For each patient, a sum score of psychiatric inpatient days during adolescence was calculated using all admissions that took place at ages 13-17. The patients were then followed up for 10 years (ages 18-27) after the index admission, or until the end of 2014, whichever came earlier. A sum score of accumulated inpatient dates during the ten-year follow-up in (early) adulthood was calculated for each patient.

Primary diagnoses were classified to externalizing disorders (F10-19, F60-69, F90-92), organic, intellectual disability, pervasive developmental disorders (F00-09, F70-79, F80-89) and G-diagnoses, schizophrenia group disorders (F20-29), severe mood disorders (F30-39), neurotic and stress-related disorders (F40-48), behavioral syndromes associated with physiological disturbances and physical factors (F50-59), internalizing disorders with onset in childhood (F93-99) and Z codes.

STATISTICAL ANALYSES

The distributions of total inpatient days during adolescence and during young adulthood were each classified to quartiles. Total inpatient days (in quartiles) during adolescence was used as the main explanatory variable. The outcome variable was inpatient treatment during follow-up that was used in the analyses as: a) dichotomized to no rehospitalization vs. any rehospitalization, and among those ever rehospitalized, b) inpatient days falling into the highest quartile vs. less than that.

Bivariate associations of length of total inpatient treatment during adolescence (classified to quartiles) as well as sex, age at index admission (13-14 years vs. 15-17 years), decade of the index admission (80's, 90's, 00's) and primary diagnosis at index admission with inpatient treatment during follow-up were explored using cross-tabulations with chi-square statistics (Fisher's exact test where appropriate).

Multivariable models were carried out using logistic regression. As the dependent variable : a) rehospitalization in 10-year follow-up (yes/no), and among those ever rehospitalized, b) high number (=highest quartile) of inpatient days in the follow-up. Independent variables used were inpatient days during adolescence (in quartiles), sex, age group at index admission, primary diagnosis and decade of index admission.

The associations between time spent in inpatient care during adolescence and inpatient treatment during 10-year follow-up were further analysed separately among those who had been diagnosed with a schizophrenia group disorder (F20-29) and those treated for other conditions at index admission.

Due to the large data size and multiple comparisons the cut-off for statistical significance was set at $p<0.01$.

RESULTS

The quartiles for the total number of days spent in inpatient psychiatric care during adolescence were as follows: 1st quartile: 0–9 days (23.9% (4032/16,842)), 2nd quartile: 10–35 days (24.1% (4051/16,842)), 3rd quartile: 36–49 days (25.3% (4268/16,842)), and the highest, 4th quartile: more than 95 days (24.8% (4181/16,842)).

During the ten-year follow-up, the upper quartile for inpatient days in adulthood was 180 days.

PATIENTS

Of the study population (n=16,842), 40.0% (n=6749) were male and 59.9% (n=10,093) female. At the index admission, 31.5% (n=5313) were aged 13–14 years and 68.5% (n=11,529) were aged 15–17 years. The distribution of primary diagnoses at the index admission is presented in *Table 1*.

A total of 14.4% (n=2427) of patients had their index admission in the 1980s, 21.0% (n=3543) in the 1990s and 64.6% (n=10,842) in the 2000s.

Table 1. Distribution of primary diagnoses at the index admission

Diagnostic group	% (n)
F00-09, F70-79, F80-89, G-diagnoses	3.0% (511)
F10-19, F60-69, F90-92	21.4% (3611)
F20-29	11.5% (1932)
F30-39	28.7% (4842)
F40-48	19.0% (3194)
F50-59	5.2% (874)
F93-99	7.3% (1233)
Z codes	2.8% (645)

INPATIENT CARE IN ADULTHOOD

Table 2 presents the occurrence of readmissions (yes/no) during the ten-year follow-up and the proportion of patients exceeding the upper quartile of inpatient days in adulthood (180 days), stratified by quartiles of inpatient days during adolescence. Readmissions were most common among those who had spent the longest time in inpatient care during adolescence (95+ days), at 30.5%. This group also most frequently exceeded the upper quartile of inpatient days in adulthood.

Inpatient care during the ten-year follow-up by index period diagnoses is shown in *Table 3*. Among those admitted with schizophrenia spectrum disorders (F20–29), 36.9% had a readmission, whereas in all other diagnostic groups the proportion was below 30% (p<0.01). This group also had the highest proportion of patients exceeding the upper quartile of inpatient days (48.6%, p<0.01), while in other diagnostic groups the proportions ranged between 15–20%.

Additionally, 27.5% (1856/6749) of males and 24.5% (2472/10,093) of females had at least one readmission during the ten-year follow-up after reaching adulthood (p<0.001). Those admitted at ages 15–17 had more readmissions (29.7%, 3425/11,529) than those admitted at ages 13–14 (17.0%, 903/5313), p<0.001. Readmissions were more common among those admitted in the 1980s (36.0%, 873/2427) compared with the 1990s (31.9%, 1129/3543) and 2000s (21.4%, 2326/10,872), p<0.01.

During the ten-year follow-up, 27.5% (511/1856) of males and 23.1% (571/2472) of females belonged to the group exceeding the upper quartile of inpatient days (>180 days), p<0.001. Among those admitted at ages 13–14, 15.0% (135/903) exceeded the upper quartile, compared with 27.6% (947/3425) of those admitted at ages 15–17 (p<0.001). By decade of index admission, 41.8% (365/873) of those admitted in the 1980s, 26.6% (300/1129) in the 1990s and 17.9% (417/2326) in the 2000s exceeded the upper quartile (p<0.001).

MULTIVARIABLE ANALYSIS

Compared with those in the lowest quartile of inpatient days during adolescence, the likelihood (Odds Ratios (OR) with 95% confidence intervals (CI)) of readmission in adulthood was higher among those with longer adolescent inpatient stays, although no linear trend was observed across quartiles: 10–35 days OR 1.2 (1.1–1.3), 36–94 days OR 1.2 (1.1–1.3), 95+ days OR 1.4 (1.3–1.6). Readmissions were also more likely among those admitted at ages 15–17 (OR 2.0 (1.9–2.2)), those with an F20–29 diagnosis at the index admission (OR 1.6 (1.4–1.7)), and those admitted in the 1980s (OR 1.7 (1.6–1.9)) or 1990s (OR 1.7 (1.5–1.8)). All ORs were statistically significant at p<0.01.

Exceeding the upper quartile of inpatient days in adulthood (>180 days) did not differ between the lowest (0–9 days) and second lowest (10–35 days) adolescent quartiles, but was more likely among those with 36–94 days (OR 1.5 (1.2–1.9)) and most likely among those with 95+ days (OR 2.3 (1.9–2.9)). Exceeding the upper quartile was also more common among those admitted at ages 15–17 (OR 2.2 (1.8–2.8)), those with an F20–29 diagnosis (OR 2.8 (2.3–3.3)), and those admitted in the 1980s (OR 2.6 (2.2–3.1)) or 1990s (OR 1.6 (1.4–1.9)). All ORs were statistically significant at p<0.01.

Table 2. Inpatient care during the 10-year follow-up by quartiles of inpatient days in adolescence

	Days in inpatient care during adolescence				
	0-9 days	10-35 days	36-94 days	95 days →	p
Readmissions during 10-year follow-up	22.4% (974/4342)	25.1% (1016/4051)	24.9% (1062/4268)	30.5% (1276/4181)	<0.01
More than 180 inpatient days during the 10-year follow-up	16.9% (165/974)	20.7% (210/1016)	24.3% (258/1062)	35.2% (449/1276)	<0.01

Table 3. Readmissions and inpatient days exceeding the upper quartile (>180 days) during the 10-year follow-up by diagnostic group

Diagnostic group	Readmission during 10-year follow-up, % (n/N)	More than 180 inpatient days during follow-up, % (n/N)
F00-09, F70-79, F80-89, G-diagnoses	24.9% (127/511)	22.0% (28/127)
F10-19, F60-69, F90-92	26.8% (969/3611)	15.1% (146/969)
F20-29	39.6% (766/1932)	48.6% (372/766)
F30-39	22.6% (1093/4842)	19.8% (216/1093)
F40-48	24.4% (780/3194)	22.3% (174/780)
F50-59	24.1% (211/874)	28.4% (60/211)
F93-99	20.6% (254/1233)	21.7% (55/254)
Z codes	19.8% (128/645)	24.2% (31/128)
p	<0.001	<0.001

INPATIENT CARE IN ADULTHOOD AMONG THOSE WITH AND WITHOUT SCHIZOPHRENIA SPECTRUM DIAGNOSES

Because patients with schizophrenia spectrum diagnoses differed clearly from all other diagnostic groups in terms of readmissions and inpatient days, predictors of adult inpatient care were examined separately for those with and without an F20–29 diagnosis at the index admission. Both primary and secondary diagnoses were included. A total of 2032 adolescents had an F20–29 diagnosis at the index admission.

Readmissions occurred in 39.3% (799/2032) of those with schizophrenia spectrum diagnoses and 23.8% (3529/11,281) of those with other diagnoses (p<0.01). More than 180 inpatient days during follow-up were recorded for 47.7% (381/2032) of the schizophrenia spectrum group and 19.9% (701/11,281) of others (p<0.01).

Table 4 shows inpatient care during follow-up by quartiles of adolescent inpatient days for those with and without schizophrenia spectrum diagnoses. Among those with schizophrenia spectrum disorders, neither the proportion of readmissions nor the proportion exceeding the upper quartile of inpatient days increased significantly as a function of adolescent inpatient days. Among those with other diagnoses, both outcomes increased with longer inpatient stays during adolescence.

Table 4. Schizophrenia spectrum diagnosis (F20–29) vs. other disorders – number of readmissions and long inpatient stays during the 10-year follow-up. % (n/N)

	Days in inpatient care during adolescence				
	0-9 days	10-35 days	36-94 days	95 → days	p
Readmissions during the 10-year follow-up • Schizophrenia spectrum (F20-29) • Other disorders	40.4% (120/297) 21.1% (854/4045)	42.0% (155/369) 23.4% (861/3682)	39.3% (201/512) 22.9% (861/3756)	37.8% (323/854) 28.6% (953/3327)	0.559 <0.01
More than 180 inpatient days during the 10-year follow-up • Schizophrenia spectrum (F20-29) • Other disorders	43.3% (52/120) 13.2% (113/854)	42.6% (66/155) 16.7% (144/861)	44.3% (89/201) 19.6% (169/861)	53.9% (174/323) 28.9% (275/953)	0.038 <0.001

DISCUSSION

The aim of our study was to examine whether the amount of psychiatric inpatient care during adolescence predicts the need for psychiatric hospitalization in adulthood, and if so, whether this is independent of age, gender, diagnosis or decade of first admission. The need for psychiatric inpatient care in adulthood was assessed over a ten-year follow-up period in terms of the occurrence of inpatient episodes and the total number of inpatient days. If an adolescent had accumulated a high number of inpatient days, readmission in adulthood was more likely and the number of inpatient days in adulthood was also higher. In addition to adolescent inpatient days, predictors of inpatient care during the ten-year follow-up included older age at entry into adolescent psychiatric care, diagnosis and earlier decade of first admission. To our knowledge, a similar analysis has not previously been conducted within the Finnish service system.

A high amount of psychiatric inpatient care during adolescence predicting extensive inpatient care in adulthood may indicate that the disorders requiring hospitalization and their symptoms were severe in adolescence and continued to be severe in adulthood. Alternatively, extensive inpatient care during adolescence may provide a pattern of emotion regulation and coping in which the young person turns to hospitalization, and this pattern may continue into adulthood. Long or repeated inpatient treatment during adolescence may also lead to stigmatization. Previous studies in both European and U.S. samples have shown that earlier adolescent psychiatric hospitalization and the accumulation of inpatient days predict future hospitalization (23,24). Repeated referrals to inpatient care may create a cycle in which the young person's sense of competence in their natural environment does not strengthen, as autonomy and self-efficacy tend to diminish in hospital settings. The phenomenon can also be considered through the dynamics of the welfare system: when a young person is frequently treated in hospital, they may learn to seek inpatient care again when a crisis escalates, and healthcare professionals may also be more inclined to refer them to hospital because of their prior admissions. This hypothesis aligns partly with labelling theory (20).

Because patients with schizophrenia spectrum diagnoses differed from all other diagnostic groups in terms of the amount of inpatient care, we also examined the predictive value of adolescent inpatient days for adult inpatient care separately for those with and without schizophrenia spectrum diagnoses at the index admission. In this analysis, schizophrenia spectrum diagnoses (F20–29) were considered both as primary and secondary diagnoses. Among those with schizophrenia spectrum disorders, the amount of inpatient care during adolescence did not significantly predict the amount of inpatient care in adulthood, whereas among those with other diagnoses, longer adolescent inpatient stays predicted more extensive inpatient care in adulthood. In schizophrenia spectrum disorders, the need for treatment is likely determined largely by the natural course of the illness rather than by external factors: these disorders are relatively chronic and persistent despite treatment, continuing into adulthood with relapses and more stable phases (25,26).

Based on the findings of this study, it is important to consider whether the need for inpatient care in adulthood could be reduced in non-schizophrenia disorders by more strongly modifying the young person's environment and strengthening their sense of competence through outpatient interventions.

Those admitted at ages 15–17 had a clearly higher risk of readmission during the ten-year follow-up than those admitted at ages 13–14. Younger adolescents may have greater potential for recovery and more remaining developmental years that support

neuroplasticity, whereas those admitted in mid-adolescence may have experienced a more severe onset of illness. For younger adolescents, symptoms may have been more strongly influenced by psychosocial factors. Additionally, the 15–17 age range coincides with the transition from compulsory education to upper secondary studies and increasing social and independence-related demands, whereas younger adolescents remain in a more structured developmental environment with less autonomy. Substance use experimentation is also more common in the older age group (27). Consistent with our findings, earlier research has shown that psychiatric disorders leading to inpatient care in young adulthood are associated with long-term and severe functional impairment regardless of the initial diagnosis (22).

Among those admitted in earlier decades, inpatient episodes during follow-up were more common than in the 2000s cohort, and particularly in the 1980s cohort, the proportion exceeding the upper quartile of inpatient days was elevated. Although those admitted in the late 2000s have had a shorter follow-up period, differences between decades likely reflect structural changes in the psychiatric care system, which has shifted toward shorter inpatient stays and a stronger emphasis on outpatient care (10). In the 1980s, the system was more hospital-centred and outpatient services were less developed.

These findings are significant for the future of adolescent psychiatric care. Extensive inpatient treatment during adolescence predicts extensive inpatient treatment in adulthood. It is important to avoid institutionalization that weakens autonomy and a sense of mastery. On the other hand, schizophrenia spectrum disorders, which require substantial inpatient care, are process disorders whose course may be less influenced by environmental factors than other disorders, which are more dependent on individual and professional interpretations and environmental influences. For this reason, future work should focus on understanding the mechanisms that explain differences in service use between diagnostic groups, and on developing diagnosis-specific risk assessment and care pathway models that account for the distinct developmental trajectories of different disorders.

STRENGTHS AND LIMITATIONS

A key strength of our study is the unselected, nationally representative register-based dataset, which is not affected by attrition. Service providers are required to report data in a standardized manner to the national HILMO register, which served as the data source for this study. On the other hand, register data do not allow examination of patients' subjective experiences regarding their need for care. The generalizability of the findings is likely limited to countries with healthcare systems similar to those in the Nordic region.

Meaningful analyses required categorizing the cumulative number of inpatients days both during adolescence and during adulthood, because in both periods the number of inpatient days was very skewed. We chose to categorize by quartiles in order to ensure sufficient number of observations in all cells. Patterns of inpatient care use have also changed over decades, so categorizations truly meaningful in content would be difficult to motivate for data over such a long inclusion period.

CONCLUSION

Extensive psychiatric inpatient care during adolescence predicts extensive inpatient care in adulthood, with the exception of schizophrenia spectrum disorders, in which the need for hospitalization is likely determined by the nature of the disorders themselves. Adolescent psychiatric inpatient care has increased in Finland over recent decades. It is essential to further strengthen support for symptom management and functional capacity in the natural developmental environments of young people with psychiatric disorders.

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ASSESSING PSYCHOTIC SYMPTOMS IN INDIVIDUALS WITH INTELLECTUAL DISABILITY

ABSTRACT

Psychotic disorders have been reported to occur more frequently among people with intellectual disabilities than in the general population. However, scientific knowledge regarding the specific characteristics and diagnostic assessment of psychotic disorders in individuals with intellectual disabilities is limited. In clinical practice, possible psychotic symptoms are often first recognized and addressed in acute situations, although a careful assessment of potential psychotic symptoms almost always requires a multidisciplinary evaluation that takes into account the individual's cognitive and emotional developmental level, other concurrent medical conditions, the aetiology of the intellectual disability and the individual's communication skills. In this review, we discuss health-related and psychosocial factors to consider in clinical assessments within the diagnostic process. In addition, we present some methods and diagnostic tools that could be used for a more thorough evaluation and psychiatric diagnosis when conducting a high-quality diagnostic process.

KEYWORDS: INTELLECTUAL DISABILITY, PSYCHOTIC SYMPTOMS, CHALLENGING BEHAVIOUR, DIAGNOSTICS

INTRODUCTION

Individuals with intellectual disability (ID) have neurodevelopmental deficits reflected in their cognitive, emotional and behavioural abilities, occurring concurrently with limitations in adaptive skills, both affect the ability for an independent life. These cognitive and adaptive deficits must originate during the developmental period, namely childhood and adolescence, but the conceptualization of ID is modified by diagnostic classification criteria used at the time. The American Association of Intellectual and Developmental Disabilities (AAIDD) function-based definition of intellectual disability emphasizes the interaction between intellectual functioning, adaptive behaviour and environmental demands and support (1). The development of adaptive skills is influenced by environmental learning opportunities and available support. Further, the AAIDD stresses that other factors such as linguistic diversity, cultural differences, as well as person's strengths should be taken into account when assessing intellectual disability (1). According to the most widely used diagnostic classification systems (ICD-10/11 and DSM-V), the severity of ID can vary from mild to profound (2–4).

The prevalence of intellectual disability is approximately 1% in the general population, even though recently there have been signs of an increase in the prevalence probably due to more efficient diagnostics (5). Psychotic disorders are defined as a spectrum of severe mental illness that include altered cognition, emotions and behaviour (6). To some extent these disorders are argued to be neurodevelopmental in nature for their course of early onset and loss of skills. Cognitive deficits in schizophrenia, a severe psychotic disorder defined as aberrant thought and perception, are evident already in childhood and adolescence, well before psychosis onset or the prodromal phase (7–9). In fact, what we call schizophrenia these days was initially described as 'dementia praecox' by Kraepelin in the early twentieth century (10). However, a unified description of psychosis is still lacking and the classification systems, such as International Classification of Diseases (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM), provide somewhat differing views to this phenomenon (6).

In this article, we do not discuss individual psychotic disorders separately, but rather address the generally presented core symptoms of psychotic disorders and their interpretation in individuals with ID. We describe the core symptoms of psychotic disorders in both classification systems (ICD and DSM) as a

background for understanding the usual approach to interpreting symptoms as psychotic. Moreover, we discuss the challenges regarding symptom interpretation among individuals with ID, because in our clinical experience, many of the classic core symptoms of psychotic disorders are described in a way that would require typically developed cognitive and verbal abilities.

In ICD-11, psychotic core symptoms include delusions, hallucinations, disorganized thinking and experiences of passivity and control. Furthermore, additional symptoms include negative symptoms, grossly disorganized or abnormal psychomotor behaviour, and cognitive, manic or depressive symptoms. In addition, updated versions of ICD-11 and DSM-V have removed the categorical approach to psychotic disorders, thus describing a more dimensional way to look at these disorders. When evaluating individuals with ID, it is useful to know and understand these different classification approaches as well as any peculiarities in these individuals' cognitive, emotional and behavioural features, in order to be able to assess them as profoundly as possible.

Not so long ago, it was thought that psychotic disorders could not occur in people with intellectual disability or autism, mainly due to lack of ability to report so-called core symptoms (11). The core symptoms, such as auditory hallucinations, thought echo, passivity experiences, thought withdrawal, insertion or broadcasting and delusional perception, indeed need to be asserted verbally in order to be detected by others. However, the absence of a mutually understandable means of communication is not a valid reason to assume that psychotic disorders cannot occur in this population. Even though research concerning psychotic disorders in individuals with ID is still scarce and mostly concerns individuals with mild ID, it is well established in the literature that co-occurrence of psychotic disorders and ID is indeed possible (12).

The knowledge on psychiatric comorbidities, including psychotic disorders, among individuals with ID is scarce. Difficulties in research on the topic are small and varying sample sizes, methodological approaches and confounding factors (13). The literature suggests that the prevalence of psychotic disorders is higher in individuals with ID than among general population. However, the prevalence alters between studies from 1.4% to as high as 7.2% (13–14), possibly indicating challenges in diagnostic evaluation among these persons. In addition, the reported rates are presented to be higher among individuals with mild ID compared to those with moderate or severe ID (14). It should be acknowledged that lower rates of psychotic disorders in individuals with severe ID might be because of the inability to make a diagnosis when it is not possible to evaluate the ideation, thoughts and feelings of a person, e.g. due to communication difficulties. On the other hand, there could be overdiagnosis of psychotic disorders among individuals with mild ID who are able to verbalize their thoughts and feelings, but are not able to express themselves in a way that they are fully understood.

Interestingly, nowadays the potential presence of psychotic symptoms is a relatively often presented hypothesis when an individual with ID is admitted to health services. Sometimes the onset of symptoms is rapid, but in some cases changes in behaviour and interaction with others have changed over a longer period of time. The term challenging behaviour is used to describe behaviour that deviates from cultural or societal expectation and causes physical, psychological, social or economic harm to the person themselves, people around them or environment (15). One of the most common forms of challenging behaviour is aggression, odd or bizarre behaviour, harming oneself or others, disrupting the environment or withdrawing from daily life activities (15–16). Challenging behaviour is stated to reflect the interaction between the person and their environment, thus indicating that it is not an individual characteristic. Therefore, challenging behaviour should always be assessed in the context in which it occurs, taking into account the perspective of the person themself as well as the perspectives of others. Challenging behaviour can occur at any age and typically peaks from adolescence to early adulthood (17), similar to severe mental health disorders (18). Yet, there are multiple factors related to the risk for challenging behaviour and psychotic disorders are only one of them.

Evaluation of psychotic symptoms in individuals with ID is not an easy task and the diagnosis of psychosis may be confounded by various factors related to, for example, communication difficulties, lack of knowledge on the aetiology and severity of ID, as well as somatic symptoms that are reflected as challenging behaviour. The known core symptoms of psychotic disorders may be interpreted as features of ID itself, but on the other hand, features of ID might be interpreted as psychotic symptoms, a phenomenon called diagnostic overshadowing (19). It should be acknowledged that in acute situations there is a primary need to try to ease patients' acute symptoms (e.g. distress, anxiety, aggressiveness) according to those methods that are available at the healthcare setting. Evaluation of the best possible approach to management of an acute situation is based on the knowledge which is available at the time. However, we emphasize that when meeting an individual with suspected psychotic symptoms in the healthcare system, the acute assessment should always be followed with more thorough multiprofessional assessment without delay.

In this article we present a thorough assessment of individuals with intellectual disability that are suspected of presenting with a psychotic disorder. In-depth assessment is based on both somatic and psychiatric factors and should always include evaluation of the primary surroundings of the person's everyday life. The assessment should also always include informants other than the individual him/herself, e.g. family members and carers who know the person well. In most of the cases, a good quality assessment should include a multiprofessional approach and teamwork (12). Clinical experience of both intellectual disability and psychiatric comorbidity is important, and hasty diagnostic conclusions may easily lead to misdiagnosis and potentially risk missing other health complaints or needs. This review aims to present factors that are important in evaluation of psychotic-like symptoms in individuals with ID, and furthermore, to present clinically relevant tools for assessing these persons.

WHAT TO TAKE INTO CONSIDERATION WHEN SUSPECTING PSYCHOTIC SYMPTOMS IN A PERSON WITH ID

When assessing potential psychotic symptoms in a person with ID, it is necessary to identify a number of factors in their personal history, especially those that may contribute to changes in their behaviour. The assessment requires both observation of the person and an interview, the collection of information from previous records, as well as interviews with the person's close relatives and carers. We have summarized the various components of a high-quality comprehensive assessment in *Table 1*. In addition, we will describe in more detail some of the aspects which, according to our clinical experience, are particularly important to identify as part of the assessment. A thorough assessment also guides decision making regarding what further investigations and assessments are justified or even necessary. The aim is to determine whether the symptoms are psychotic or whether the behavioural change is, for example, a reaction to other factors relating to the person's health or their psychosocial environment.

Table 1. Factors that should be considered when evaluating a person with ID presenting with psychotic-like symptoms

Background information on intellectual disability • Aetiology and severity of the intellectual disability • Aetiology and the investigative methods used to determine it, if the aetiology remains unclear • Stage of emotional development
Somatic factors • Concurrent medical conditions and the balance of their treatment, particularly epilepsy • Pain conditions (e.g. dental pain/oral health, increased spasticity) • Current medication and medication history, including past history of harmful side effects • Changes in sensory functions (particularly vision and hearing) • Alcohol and other substances use • Nutrition (regularity, quality, caffeinated products, dietary supplements)
Daily life and functional ability • Daily routine and activity (whether they attend a day centre, work programme, school or after-school care) • How their developmental disability and its characteristics (e.g. sensitivity to stress, sensory hypersensitivity, sensory impairments) are taken into account in daily life at home or in other everyday settings • Routines and rituals (targeted daily rhythm, morning and evening routines appropriate to their developmental level) • Modes and aids for communication and interaction • Executive functioning
The progression of symptoms • Changes in behaviour and the progression of symptoms • The significance of symptoms to the persons themselves • The significance of symptoms to those around them • Possible triggering factors underlying the symptoms (losses, changes, etc.)

A person's psychosocial environment and support • Family members, loved ones, friends, carers • Living environment and the services provided within it • Healthcare contacts and follow-up, e.g. the developmental disabilities outpatient clinic • Social work contacts • Opportunities to influence and participate in decision making
Psychiatric conditions • Previous diagnostic procedures, including the use of methods designed for patients with ID • Balance of treatment (pharmacological and psychosocial), means of follow-up • Sleep-wake cycle disorders

AETIOLOGY OF INTELLECTUAL DISABILITY

Based on their underlying aetiology, intellectual disabilities can be broadly categorized into three groups: 1) genetic disorders and syndromes (e.g. Down syndrome, Fragile X syndrome), 2) acquired conditions associated with prenatal factors (e.g. infections and teratogenic exposures), perinatal factors (e.g. birth asphyxia) or postnatal factors (e.g. traumatic brain injury, severe malnutrition or toxic exposures) and 3) conditions of unknown aetiology (20–21). Socio-environmental factors, such as access to services (e.g. access to healthcare and social services), home learning environment (e.g. enriched home environment, opportunities to play and learn, parent-child interactions), parental stress and parental mental health problems and learning opportunities (e.g. access to special education, parental education, intervention services) are also associated with cognitive and adaptive functioning in individuals with intellectual disability (22).

The heterogeneous aetiology presents with varying phenotypes regarding somatic and psychiatric illness, trajectories of cognitive and emotional development, behaviour and communicative abilities (5). Therefore, when suspecting psychotic symptoms in an individual with ID, it should always be confirmed whether the aetiology is known, what kind of aetiological studies have been conducted and when (and are they considered currently relevant and according to current methodology). This is especially important in such situations when the aetiology is not known, and the aetiological studies have been conducted years ago, e.g. in childhood. There are new methods and rapidly increasing knowledge of different aetiologies regarding genetic variations behind different phenotypes of ID. Thus, it should be considered whether aetiological studies be expanded to, for example, exome sequencing (23), especially when the individual presents with new symptoms that affect greatly their functioning and wellbeing. A consultation with a medical geneticist is recommended when in doubt. If the aetiology is known, it should be determined without delay whether this specific aetiology includes heightened risk for psychotic disorders, or for other factors that might be falsely presented and interpreted as psychotic symptoms.

Some genetic syndromes have specifically been associated with increased risk for psychotic disorders. The most commonly known syndrome is 22q11 deletion syndrome, (DiGeorge syndrome), that presents with typically mild to moderate ID and psychosis developing in approximately 40% of individuals (24). In addition, it has been stated that the risk of psychosis is higher in Klinefelter syndrome (25) compared to general population.

As important as it is to know if there is or isn't increased risk for developing psychosis in a specific ID disorder, it is also important to know what other neuropsychiatric features might be associated with the given syndrome. For example, there is an increased risk for early dementia in Down syndrome, which might be confused with negative symptoms or even psychotic catatonia if the diagnostic evaluation is left too superficial. Onset of regression linked to dementia might be detected already at very early age, between 20-30 years of age (26).

COGNITIVE PROFILE AND SEVERITY OF INTELLECTUAL DISABILITY

Intellectual disability is classified into mild, moderate, severe and profound intellectual disability, based on an assessment of cognitive ability supplemented by an evaluation of adaptive skills (2–4). When assessing possible psychotic symptoms, it is advisable to determine whether the severity of the developmental disability has been defined or whether the diagnosis is an unspecified intellectual disability. Further, it is recommended to consider the individual's cognitive profile, particularly their level of concrete thinking. The diagnostic evaluation may become distorted if concrete responses, reflecting language and thinking characteristics, are interpreted as psychotic thoughts. However, it is noteworthy that neuropsychological assessment should not be conducted during the acute phase of a suspected psychotic episode.

Information regarding the cognitive strengths and weaknesses provides insight into how and at what developmental

level the individual perceives and interprets their environment, as well as their ability to perceive signals from their own body and mind. Especially in stressful situations, an individual's ability to distinguish and interpret signals from the environment, body and mind is disrupted. People with developmental disabilities have been found to be more sensitive to psychological stressors than the general population, which likely contributes to the occurrence of challenging behaviour in them (27).

However, the severity of the developmental disability alone does not provide sufficient insight into the individual's cognitive ability profile; whenever possible, it is advisable to examine this profile more closely. For example, significant difficulties with perception can cause a significant increase in stress for an individual whose daily life involves new and changing environments and situations. This can lead to reactions that an outsider might interpret as disorientation or even psychosis, even though the issue is simply a person with a developmental disability being placed in an environment where demands exceed their skill level.

EMOTIONAL DEVELOPMENT

Knowledge of the individual's stage of emotional development can be helpful in interpreting and diagnosing observed aberrant behaviour of patients with ID that may be suspected to be psychotic. Emotional development refers to the differentiation and regulation of emotions, as well as the development of interaction and attachment relationships (28–29). Research indicates that, in individuals with intellectual disability, emotional development typically corresponds to a markedly earlier developmental stage compared to cognitive functioning and adaptive skills (29). The stage of emotional development in individuals with intellectual disability and/or autism spectrum disorder can be assessed using informant-based interview instruments called the SEO R2 and SEED-2 (30–32). This information can help to determine whether a person's behaviour is consistent with their stage of emotional development (even though it is not consistent with their chronological age or cognitive level) or whether it deviates in a way that may indicate possible psychosis. For example, an individual may expect a celebrity to arrive and even report having spoken with that person, which could be interpreted as a disturbance in reality testing. However, from the perspective of emotional development, this behaviour may instead reflect an earlier stage of emotional development and difficulty in distinguishing wishes and fantasies from everyday reality.

CONCURRENT MEDICAL CONDITIONS

Physical vulnerability is a term often used to describe individuals with ID who are more prone to different somatic complaints. Many of these somatic conditions are associated with ID and varying aetiology (17). It has been observed that the identification and treatment of somatic symptoms in people with ID are often delayed, in part because they are unable to express their symptoms or communicate their need for an evaluation. People with ID could actually need more health checks than the general population, but commonly health checks are delayed or even neglected. At its simplest, the assessment may reveal very common and easily treatable somatic conditions, such as constipation, which can cause significant discomfort for the individual. This discomfort itself can very easily manifest as alterations in emotional and behavioural regulation of a person with ID. Therefore, even the treatment of a very simple and ordinary somatic issue can, at best, significantly reduce challenging behaviour and allow the individual to function and interact in a manner that is typical for them. Thus, one of the key aspects to be checked first when evaluating psychotic-like symptoms of any kind in patients with ID is assessment of patient's general physical health. Pain, constipation, problems in oral and dental health are common reasons for altered behaviour in patients with ID (17,33), and it would be questionable to conclude that a patient suffers from psychotic symptoms if the underlying cause is, for example, untreated dental pain to which the individual is reacting.

More complex and demanding common concurrent medical conditions that often require cross-disciplinary assessments include: epilepsy, sensory disability, obesity and cardiovascular diseases (17,33). Individuals with intellectual disabilities experience all of these conditions more frequently than the general population, but on the other hand, recognizing and treating these somatic problems is often more challenging for them.

Particularly with regard to epilepsy, it is important to consider the challenges the condition presents to the patient's functioning and emotional and behavioural regulation. Additionally, it is important to be aware that medications used for treating epilepsy may have side effects that contribute to challenging behaviour, such as increased sleep disturbances, impulsivity and irritability. Furthermore, syndromes associated with intellectual disabilities also carry an increased risk of severe epileptic syndromes, where achieving treatment stability is often very difficult. Drug-resistant epilepsy is a problem especially associated with severe and profound ID (34).

Obesity is more common among individuals with ID compared to the general population, and significant obesity typically occurs from childhood and adolescence onward. Obesity, along with the structural abnormalities often associated with ID syndromes (such as narrow airways), particularly predisposes individuals to sleep disorders such as sleep apnoea (35–37). Additionally, obesity combined with antipsychotic medication treatment, often related to challenging behaviour in individuals with intellectual disabilities, can lead to an increased risk of metabolic side effects from long-term use. Obesity itself is associated with musculoskeletal symptoms and decreased mobility, which in combination, can readily lead to the development of various musculoskeletal pain conditions (38–39).

The risk for cardiovascular diseases has been reported higher among individuals with ID than general population. The risks seem to be elevated especially when the patient has antipsychotic medication (40). Unfortunately, the monitoring and follow-up of electrocardiograms (ECG) in relation to medication is often inadequate for patients with ID, mostly due to problems of cooperation and communication. Similarly, simple blood pressure measurements are commonly neglected, even though necessary especially in older patients. Preparation for such examination often requires more time than usual, and augmentative communication aids should be used so that the patient would know what is expected of him/her. The need for management of cardiovascular risk factors, such as hypertension, should be better acknowledged in individuals with ID due to their increased risk for severe outcomes and misdiagnosis (40).

Sensory disabilities, such as vision impairment and progressive hearing loss, are more common among individuals with ID than others and should therefore be regularly assessed (41). Surprisingly, deficits in hearing are often unrecognized even though hearing is crucially connected to quality of life. In the study by Zielonkowski et al. 2025, it was found that 44% of the study participants with ID had deficits in hearing, with only 25.9% of them being previously known to have a hearing disability (42). Hearing or vision impairment may manifest as changes in an individual's behaviour, such as increased fear, heightened caution, sensitivity and sudden reactions to changes in the environment. Gradually, the decline in sensory function may lead to withdrawal from situations that were previously ordinary and familiar, but now feel unsafe and threatening. This may present as apathy or flattened, withdrawn behaviour for which there is no apparent explanation. On the other hand, changes in sensory function can also result in situational challenges, leading to sudden changes in behaviour. For example, if a person does not hear someone approaching, they may startle when that person unexpectedly enters their field of vision. In response to this sudden stimulus, an individual with ID may react very strongly, even in a way that may be interpreted as aggressive or threatening. If a decline in sensory function is not recognized, it becomes difficult to prepare for situations in a way that would allow an individual with ID to respond to changing circumstances more calmly and predictably.

Beyond the concurrent medical conditions mentioned, there could be many other somatic complaints that should be considered. Therefore, the aetiology and individual's past medical history should be checked as well as possible, in order to plan further examinations and treatment according to individual needs.

PHARMACOTHERAPY

A careful investigation of patient's history of pharmacotherapy is important when evaluating possible psychotic symptoms and underlying factors. It is well documented in literature that patients with ID have considerably higher levels of pharmacotherapy and polypharmacy compared to patients with no ID (43).

For example, antipsychotic pharmacotherapy is relatively common in treatment of challenging behaviour (44), even without a diagnosis of psychotic disorder. However, in clinical experience it is seen that patients with ID are more prone to side effects and are commonly treated with off-label pharmacotherapy. In addition, systematic follow-up of harms and benefits is unfortunately often neglected with patients with ID due to difficulties in cooperation (e.g. difficulties in getting blood samples) and lack of instruments for interviewing about patient experiences regarding the medication use.

It is documented that ageing and associated tiredness, fatigue and multiple somatic disorders arise at a younger age among individuals with ID than in others (45). Thus, it could be suggested that premature ageing has an effect on changes in pharmacokinetics and pharmacodynamics, similar to ageing in general but just at younger age in individuals with ID: the risk for early Alzheimer's disease and early menopause are especially associated with Down syndrome (46–47).

From a clinical perspective, polypharmacy causes challenges in evaluating both symptoms and also possible negative or harmful effects of pharmacotherapy itself as a potential cause for symptoms that present as psychotic-like features: presentation of negative symptoms could be a side effect of antipsychotic medication use (e.g. extrapyramidal syndrome) than a sign of psychosis. Due to the quite modest number of studies on treatment of psychotic symptoms in

individuals with ID, it is also recommended to see through case reports as a potential source of clinical cues, especially when the aetiology of ID is known. For example, a case report shows a patient with Williams syndrome, who was interpreted to present with psychotic symptoms and thus treated with high-dose antipsychotics. The patient developed a malignant neuroleptic syndrome and by diminishing all antipsychotic medication the patient's state improved so that the severe side effect and also the initial psychotic-like symptoms were gone. The unusual trajectory of both psychotic symptoms and also the response to medication was hypothesized to associate with the genetic profile linked to the aetiology (48).

EXECUTIVE FUNCTIONS AND SELF-TALK

Many individuals with intellectual disability often talk out loud or whisper to themselves, which can be considered a form of self-talk or private speech. Self-talk is highly prevalent in persons with Down syndrome, with studies reporting approximate rates of 80–90% (49–50). Self-talk is commonly observed in typically developed young children between approximately 2 and 7 years of age and it supports the development of self-regulation and executive functions (51). Through self-talk, children guide their own actions, behaviour and emotions during tasks and problem-solving situations. In typical development, self-talk decreases with age as it becomes internalized into inner speech during the school years (51). One form of self-talk involves speaking to or interacting with imaginary friends, which are a common and developmentally typical aspect of childhood (52). In adolescents and adults with intellectual disability, self-talk may reflect an early level of development in self-regulation and executive functioning. Further, many adolescents and adults with intellectual disability have imaginary friends, especially individuals with Down syndrome (50). Therefore, it is very important to differentiate whether the behaviour represents self-talk or a manifestation of psychotic symptoms.

MODES OF COMMUNICATION

From the perspective of interaction and communication, altered behaviour can be a sign of a person's need to be understood and heard, rather than a symptom of psychiatric disorder. Therefore, it should always be assessed what the means of communication are of the given person and how they are applied in everyday life by patients themselves, and also the people around them.

Augmentative and alternative communication (AAC) can be used with individuals with ID and other developmental disabilities with complex communication needs. AAC includes unaided systems (manual signs and gestures) and aided systems (technical devices and applications designed specifically for AAC), and AAC interventions are known to increase functional communication skills, language and social competence. In addition, using AAC has shown to increase natural speech (53). When evaluating a patient with communication deficits there should always be suitable communication aids used, and if none are recognized, a consultation with an AAC professional, speech therapist or other professionals familiar with intellectual disability to check possibilities to add other AAC methods to the evaluation. Relatively easily available communication aids, such as using pictures, quick drawing and building social stories can be used to support, for example, a psychiatric interview.

CONCURRENT PSYCHIATRIC CONDITIONS

For psychiatric differential diagnosis, the most relevant disorders to consider are other neurodevelopmental disorders, such as autism spectrum disorder (ASD) (54) and attention deficit hyperactivity disorder (ADHD) (55). There is strong evidence of a markedly increased risk of psychotic disorders among individuals with intellectual disability, and also among individuals with ASD. Prevalence of co-occurrence of ASD and psychotic disorders is estimated to be as high as 35% (56) and for ADHD and psychotic disorders 18.5% (57). However, the co-occurrence of other neurodevelopmental disorders with ID does not necessarily indicate higher likelihood of psychotic disorder, but rather it underscores the need for a careful and thorough assessment of symptoms and their underlying causes. Overlapping symptoms and diagnostic overshadowing in these disorders and intellectual disability is common. Until recently, there has been a lack of diagnosing comorbid neurodevelopmental disorders because it has been thought that all deficits in executive functioning, social interaction or attention could be explained well enough by the intellectual disability itself. Lastly, it is useful to know that a diagnostic tool for assessment of ADHD in individuals with ID has been developed. DIVA-ID includes concrete, real-life examples linked to the features of ADHD in individuals with ID to help in the assessment (58). Validation processes for different language versions are ongoing, and to date, data regarding use of this instrument still remains modest.

Assessment of personality disorders (PD) as potential differential diagnosis should be considered only through careful evaluation and understanding of the cognitive and emotional developmental stage of the patient. Regulation of emotions and behaviour can reflect delays in emotional and cognitive development rather than pure personality disorder. In fact,

the diagnosis of personality disorder in individuals with ID is described as contentious due to the fact that individuals with ID indeed present with inadequate development of cognitive and also emotional functioning (59). Over time, clinicians have debated whether personality disorders can be diagnosed during adolescence, when brain development is still significantly underway, or if the diagnosis of personality disorders should be reserved for a more developmentally mature stage, such as adulthood. Indeed, personality can be conceptualized as the lasting characteristics influencing a person's thoughts, feelings and behaviour, thus shaping a person's way of interacting with others. Personality disorder refers to a state where these characteristics significantly impair a person's wellbeing and social functioning in the long term, and thus does not usually illustrate an acute change in a person's emotions and behaviour (60). Currently, a diagnosis of personality disorder is generally made in late adolescence and adulthood. The prevalence of personality disorders among individuals with ID varies greatly between studies, with antisocial personality disorder being the most common, and unspecified personality disorder presenting as the second most common form of PD (17). Many of the studies have been conducted in forensic settings, and in secure intellectual disability services PD has been reported to be even as high as 50% (59). However, it can be hypothesized that the very high prevalence in literature is biased, e.g. due to study settings (only forensic psychiatry patients) or due to highly variable diagnostic practices.

Diagnosing personality disorders typically necessitates the person to have insight into their own thoughts and emotions, which can be challenging to obtain in individuals with ID. Furthermore, when it comes to borderline or dependent personality disorder, it is important to understand that individuals with ID are more reliant on caregivers than others due to their disability, and it might be hard to distinguish so-called normative from pathological expectations in close relationships. Lastly, antisocial features of personality should include a thorough understanding of the individual's ability to cognitively understand and process norms and laws, as well as causal relationships with actions and outcomes (61). These are examples of difficult entities that should be assessed when evaluating possible personality disorders in persons with ID as one possible differential diagnosis for psychotic symptoms and even disorders. Diagnosis of personality disorders among patients with ID is a challenging task and should be restricted to those professionals who have experience in both ID and psychiatry.

Furthermore, affective disorders should also be considered as potential differential diagnosis for patients with ID who present with altered mood and emotion regulation. However, these disorders should always be assessed with thorough understanding of patient's trajectory of life history, including pharmacotherapy. A Swedish register-based study implied that the rates for affective and anxiety disorders seem to be 11 times higher in individuals with ID than others. In addition, an unspecified non-organic psychosis was reported as a common psychiatric comorbidity with affective and anxiety disorders. Affective and anxiety disorders have many similar features when it comes to symptoms, and there is probably some overlapping of the symptoms among these phenomena. Regarding register-based studies, it is difficult to know the diagnostic procedure behind the diagnoses. We hypothesize that many of the psychiatric diagnoses for individuals with ID have been set in acute settings, due to lack of long-term follow-up, and treatment in clinical settings that would have experience in both ID and psychiatry. In addition, many of the psychiatric diagnoses are left unspecified, reflecting the difficulty of accurate differential diagnosis in individuals with ID (62).

A careful psychiatric examination of a patient always includes a general psychiatric investigation, not only looking into a given symptom or suspected pathology. Further, we present some tools to facilitate psychiatric examination in this patient population concerning not only psychotic symptoms but other psychiatric phenomena.

MEANS OF INVESTIGATION AND EVALUATION

If, on the basis of a thorough interview and assessment, no primary explanatory factors for the change in behaviour emerge from the patient's background, the assessment should proceed to a more detailed psychiatric differential diagnosis. When proceeding to the actual psychiatric differential diagnosis in the assessment of a person with ID, it is important to have a good understanding of how the person's typical wellbeing, functioning and way of interacting with their environment are characterized. For example, intellectual disability itself may be associated with significant motor restlessness compared to non-disabled individuals, but also notable slowness and rigidity. This should be taken into account particularly regarding motor symptoms and altered functioning in relation to the person's previous physical condition, mobility and ability to cope independently.

Assessment tools have been developed for the psychiatric assessment of people with intellectual disabilities, based on commonly used diagnostic classification systems (the ICD and DSM classification systems). When using these instruments, it

is very important to also utilize alternative and augmentative communication aids, particularly in situations where the aim is to ascertain from the person themselves their symptoms and what these mean in their daily life.

The handling of the following assessment methods is necessarily somewhat exemplary in this context, as the diagnostic evaluation of a patient with an intellectual disability must consider the means used on a very individual basis, particularly in relation to communication methods. However, it is crucial to understand that such aids and methods have been developed to support diagnostic evaluation, and their use is recommended.

Adaptations of the most commonly used diagnostic criteria have been designed specifically to support the diagnostic processes concerning individuals with ID. Diagnostic Manual—Intellectual Disability (DM-ID): A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability is based on both evidence-based methods and the expert-consensus model. It covers a broad examination of the topic, with a description of each disorder and a summary of the DSM-V diagnostic criteria. DM-ID also includes a review of the literature and an evaluation of the strength of evidence supporting the literature conclusions, a discussion of the aetiology and pathogenesis of the disorders and adaptations of the diagnostic criteria for the ID population. DM-ID has been developed as adaptation of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition—Text Revision (DSM-IV-TR) by The National Association for the Dually Diagnosed (NADD), in association with the American Psychiatric Association (APA) (61).

The Psychopathology in Autism Checklist (PAC) (12) is a validated instrument that has been used to assess psychotic symptoms in patients with ID and autism spectrum disorder. It encompasses five subscales and 42 items: general adjustment problems (GAP) 12 items, psychosis 10 items, depression 7 items, anxiety 6 items and OCD 7 items, and therefore serves as a method for larger differential diagnosis. PAC is a carer-completed instrument for screening possible psychiatric symptoms, including psychotic symptoms. The carer as an informant could be a family member or a professional carer. However, the most important thing is that to be able to report any changes in individual's mood and behaviour, the informant has to know the assessed individual well. PAC has been shown to discriminate well between individuals with ID and autism with and without psychiatric symptoms (63).

Psychiatric symptoms can also be assessed by using the Moss-PAS (ID), which is an informant-based semi-structured interview that covers seven different psychiatric symptom categories (depression, anxiety, elevated mood and hyperactivity, obsessive compulsive disorder, psychosis, possible organic disorders, autism). The Moss-PAS (Diag ID) is a more comprehensive assessment tool, designed for individuals with ID who have enough verbal skills to be interviewed regarding their own symptoms with a semi-structured interview (64). The Moss-PAS diagnostic tools are adaptations of ICD and DSM classifications with the latest updates from ICD-11 and DSM-V diagnostic criteria (65).

Other diagnostic tools designed for general population can also be used to assess individuals with ID. Diagnostic tools in assessing psychotic disorders in individuals with ID are described thoroughly by Bakken (12). However, when using structured or semi-structured interview, it should be acknowledged that the patient might have limitations in understanding complex questions and expressing inner sensations, thoughts and emotions. AAC methods are recommended to support communication with the individual, and the chosen method of examination should always be selected based on the patient's cognitive abilities. Self-report questionnaires are typically not useful in psychiatric examination of individuals with ID and should only be used as a basis for interview. Thus, a good-quality informant is an extremely crucial factor in the careful assessment of symptoms.

DISCUSSION

Psychiatric diagnosis in individuals with intellectual disabilities is challenging and often requires a thorough multidisciplinary assessment. We acknowledge that the presented approach is likely to be time-consuming and requires in-depth knowledge and experience regarding psychiatric differential diagnosis in individuals with ID. However, we would like to emphasize the fact that before assessing actual psychotic symptoms, it is important to consider whether the more common causes of challenging behaviour have been ruled out. This is especially important among these patients who lack the abilities and opportunities to express themselves without communication aids. In cases of acute symptoms, one must, of course, act in accordance with the principles that ensure the safety of the patient and their environment, and in such cases, more extensive investigations may have to wait—but they should not be forgotten.

Information regarding psychotic disorders in individuals with developmental disabilities and their differential diagnosis remains quite scarce (12). To support clinical assessment, it is therefore important to seek information and assistance from a variety of sources, transcending the boundaries of specialized fields. It is important to reflect the assessment of behaviour

and interaction against the person's cognitive and emotional developmental stage and to take into account the aetiology of the developmental disability and its possible specific characteristics.

We want to emphasize that it is naturally possible to reach a situation in which the diagnosis of a psychotic disorder is justified. Just as it is important not to diagnose something that is not a psychotic illness as such, it is equally important not to dismiss a condition that meets the diagnostic criteria for a psychotic disorder as merely challenging behaviour. It is essential that individuals with intellectual disabilities are diagnosed with the psychiatric disorders they suffer from, which significantly impact their functioning. Careful diagnosis enables appropriate treatment and follow-up, as well as increasing knowledge and understanding of mental health disorders in individuals with intellectual disabilities. Therefore, this review, with its numerous perspectives to consider, serves as a crucial description of the factors that can lead to the identification of a psychotic disorder, or another possible reason, behind altered behaviour.

Through careful assessment, psychotic disorders in individuals with developmental disabilities can be better identified and diagnosed than before. Furthermore, a careful assessment ensures that phenomena and symptoms that can be explained by the developmental disability itself or by other somatic or psychiatric factors are not misinterpreted as psychotic symptoms.

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SOMATIC PHYSICIANS IN PSYCHIATRIC INPATIENT SERVICES: A NARRATIVE REVIEW

ABSTRACT

***Background**: Individuals with severe mental illness experience a high burden of somatic comorbidity, while psychiatrists in psychiatric settings may face challenges in providing adequate somatic care for their patients. Integrating somatic physicians (SPs) into psychiatric inpatient services has been proposed to improve the quality of care.* ***Methods**: This narrative review examines original research on SP involvement in psychiatric inpatient settings by a literature search from studies published between 1995 and 2026.* ***Results**: We identified twelve studies from four decades describing heterogeneous service models. SPs contributed to generating, reviewing and organizing information on patients' somatic health, management of acute and chronic somatic conditions, health promotion and coordination of follow-up and transitions to primary care. Staff and patient experiences were generally positive, highlighting collaboration and improved access to somatic expertise. SP involvement enhanced continuity and organization of care, and strengthened interprofessional collaboration. Findings regarding economic outcomes were limited and inconclusive. Patient-reported outcome measures were not assessed in the included studies. Psychiatric inpatients' need for support in somatic care, continuity of post-discharge somatic care and clarification of professional roles were considered as challenges.* ***Conclusion**: While research on integrated somatic care in psychiatric inpatient settings remains limited, the included studies report promising but scattered findings of integrating SPs to support holistic psychiatric inpatient care. The need remains for further research on the impact of different SP models for care processes and health outcomes. Establishing ongoing interprofessional dialogue and cultures of collaboration emerged as an important topic, both for further research and the practical work of adapting various SP models to different contexts of care.*

KEYWORDS: SEVERE MENTAL ILLNESS, SOMATIC COMORBIDITY, INTEGRATED CARE, QUALITY OF CARE, HEALTHCARE, INPATIENT, GENERAL PRACTITIONER, HOSPITALIST

INTRODUCTION

It is well known that somatic comorbidity shortens the lifespan among individuals with severe mental illness (SMI) (1,2). The interplay between psychiatric symptoms, health-related behaviour, medication side effects, difficulties in self-care, low socioeconomic status and experience of distress and stigma endanger somatic health and wellbeing in this group (3,4). In addition, individuals with SMI face numerous barriers in accessing healthcare and in getting adequate treatment for somatic illnesses (5,6). Accordingly, during their treatment in psychiatric services patients with SMI also present with several acute and long-term somatic illnesses and accumulated risk factors needing attention (7,8).

Attending psychiatrists are, by definition, responsible for the treatment of patients in psychiatric wards, including basic somatic care (9). However, psychiatrists may feel unfamiliar with providing treatment for acute and chronic somatic illnesses (10–12). Time constraints due to daily psychiatric practice and limited possibilities to update general practice skills make the call for holistic care hard to handle.

The inequity related to the burden of somatic comorbidity among individuals with SMI, and shortage of real-world solutions to tackle it, have been evident for a long time. Development of new health service models that would improve status praesens are urgently needed. While an integrated care model of consultation-liaison psychiatry offers care for patients in somatic units (13), somatic resources dedicated explicitly for psychiatric patients exist only sporadically (12,14).

In this review, we focus on an emerging service model in the delivery of healthcare for individuals with SMI: integrating somatic physicians into psychiatric inpatient settings. Research regarding integrated somatic care within psychiatric services has focused primarily on outpatient settings (15,16), whereas the unique review on inpatient studies dates back to 2010 and was able to include only four peer reviewed papers (17).

According to the literature, three types of somatic physicians (SPs) have been involved in psychiatric inpatient care: general practitioners, hospitalists and internists. Of these three categories, general/family practitioners and family doctors (hereafter GPs) work with hospitalized patients to some extent. The second category, hospitalists, usually refers to physicians specialized in hospital medicine, a medical specialty practiced predominantly in North America. Hospitalists typically consult and coordinate care in both somatic and psychiatric wards, and are involved in systems-level improvement in large hospitals (18). Third, physicians specialized in internal medicine have been involved in the treatment of psychiatric inpatients. In this review, we use the term SP to refer to GPs, hospitalists and internists.

PURPOSE OF THIS REVIEW

*SP*s may have potential in improving the quality of care for psychiatric inpatients and in alleviating the workload of psychiatric staff. In this review we summarize, to the best of our knowledge, existing publications of empirical studies regarding SP services in psychiatric inpatient settings. We aim at offering evidence-based support for considering integrated somatic inpatient services in psychiatry and formulating new research questions.

METHODS

During the project, we conducted multiple unsystematic literature searches addressing SPs working within psychiatric inpatient settings. In addition, we conducted reference list screening and forward citation tracking. In order to find possibly missed studies, we also executed literature searches from PubMed, CINAHL, Web of Science and Scopus AI of studies published between 1995-2026 (see *Supplement* for further information).

Since the articles retrieved in the preliminary searches with our search term combinations yielded a large quantity of material with no connection to our scope, we used AI to select suitable search terms. Scopus AI- and ChatGPT-assisted database search term query development resulted in having one category for the role of the somatic physician/model and another for the clinical setting, which was eventually used as the search term combination: *hospitalist* OR gp* OR "general practitioner*" OR physician* OR "generalist physician" OR "medical comanagement" OR "collaborative care" OR "somatic care" OR "medical consultation" OR "somatic consultation" OR "collaborative care" OR "integrative care" AND ("psychiatric inpatient" OR "psychiatric hospital" OR "psychiatric inpatient unit" OR "mental health ward")*. The term gp* was omitted when the searched database rejected it as too short a search term.

We assessed the relevance of publications identified by the searches based on their titles and abstracts. Criteria for inclusion were: 1) original empirical peer-reviewed articles and conference papers, 2) published between 1995–2026, 3) written in English, 4) focused on SP clinical work and its outcomes, 5) within a psychiatric inpatient setting. All study designs were allowed. Policy papers and grey literature were not included. Articles were excluded if they did not meet the inclusion criteria. In unclear cases, the relevance of articles was discussed jointly by the research team.

LITERATURE REVIEW

We identified twelve original studies, including one conference paper (19), examining SP services in psychiatric inpatient settings (*Table 1*). There were two qualitative papers (20,21) and one randomized controlled trial (22), while most were descriptive quantitative studies. Four studies included comparisons of outcomes/features before and during SP involvement (22–25).

Half of the included papers reported a piloting phase of the service, while two (21)(25) examined a modification of a permanent model. The hospital environment was specified as free-standing psychiatric hospital in three studies (21,23,26) and as a psychiatric ward residing in somatic campus in two (27,28). All studies, except two (26,29) were conducted at university hospitals.

After identifying the included studies, we conducted an initial summarization of the studies, focusing on research context, study topics, the scope of the SP role, and findings related to experiences and effects of implementing the SP model (*Table 2*). Through further rounds of inductive content analysis, we identified six relevant themes in the original studies regarding SPs in psychiatric inpatient settings: context, resourcing and role; SP responsibilities in the care process; staff and patient experiences of services; systems-level changes; economic

aspects and challenges in implementing the service (*Table 3*). Our review of these themes is reported in the following sections.

Table 1. Twelve original studies that were included in the review

Author, year	Country	Method	Data source	Setting
Fisher and Roberts 1998 (26)	UK	Descriptive quantitative study.	Medical records from four years of residing patients in the unit*.	GP visiting a psychogeriatric long-stay unit twice a week.
Welthagen et al. 2004 (29)	UK	Descriptive quantitative study.	Medical records from 84 appointments, 18 patient interviews.	GP visiting three acute wards and a small psychogeriatric service three hours per week.
Rubin et al. 2005 (22)	US	Randomized controlled trial.	Records on elements of care and of hospital charges from 55 patients (+ 84 in the control group).	Internist working at two acute psychiatric wards full-time.
Saik et al. 2007 (25)	US	Descriptive quantitative study.	Survey of 24 psychiatrists and 65 nurses. Regulatory compliance reports	Internist responsible for patients' non-psychiatric medical care.
Behroozi et al. 2008 (27)	Canada	Descriptive quantitative study.	Medical records from 40 patients, surveys from 28 staff members.	FD visiting two acute wards and a short-stay area on weekdays.
Goh et al. 2015 (23)	Australia	Descriptive quantitative study.	Medical records from165 patients.	Medical resident working at an acute psychogeriatric ward half-time.
Tatreau et al. 2016 (24)	US	Descriptive quantitative study.	Medical records from 220 patients (+ 232 in the control group).	FP supervising a physician assistant, available remotely five days a week for one unit.
Mc Cracken et al. 2018 (28)	Canada	Descriptive quantitative study.	FD self-report from 104 consultations.	Four FDs from an outreach clinic, available four half-days a week for four wards.
Wolsing et al. 2024 (20)	Denmark	Qualitative study.	Interviews from 17 patients.	Medical doctors conducting health examinations in psychiatric wards.
Bloom-Feschbach et al. 2025 (21)	US	Qualitative study.	Surveys from eight (first round) and five (second round) hospitalists, ten psychiatrists and one nurse practitioner.	Full-time director hospitalist on weekdays and on call. Nine hospitalists, each one day a week at site and four days remotely. When the director hospitalist is absent, hospitalists on call. 24/7 coverage in a large psychiatric facility.
Mårtenson et al. 2025 (19)	Finland	Descriptive quantitative study.	GP self-report from 245 assessments.	Three GPs available for 17 wards part-time.
Nissen et al. 2025 (30)	Denmark	Descriptive quantitative study.	Questionnaires, anthropometric measurements and laboratory tests from 238 patients.	Internist conducting health examinations in psychiatric wards.

Note: GP=general practitioner, FD=family doctor, FP=family practitioner
* At the beginning there were 44 patients at the unit. During the period of four years 21 patients died, 14 new patients were admitted and three discharged

Table 2. Key findings of the included studies (n=12)

Author, year	Key findings relating to the review
Fisher and Roberts 1998 (26)	*SP role*: Assessment and management of physical health problems, with specialist referrals when needed. The SP mainly managed cardiovascular, dermatological, musculoskeletal and ENT conditions, conducted risk screening and health promotion, developed annual health checks and addressed medication overprescription. *Patient experiences of SP*: Patients valued the service, developed trust in the SP, and accepted physical examinations. *Effects of SP model*: Physical health summaries were prepared and regularly reviewed. *SP model feasibility*: The study highlighted the need for dedicated SP services in psychiatric wards and suggested they may be cost effective, particularly in larger units.
Welthagen et al. 2004 (29)	*SP role*: Referral-based service managing a broad range of physical health problems, especially endocrine, musculoskeletal, dermatological, genitourinary and cardiovascular conditions. The SP also managed hypertension and diabetes, identified serious undiagnosed illnesses, provided risk-factor screening, health promotion and educated both patients and staff. *Patient experiences of SP*: Patients were generally satisfied, valuing the SP's professionalism, kindness and accessibility, though some would have preferred their own GP and wanted better access to and information about the service. *SP model feasibility*: The study supported the need for primary care expertise in acute psychiatric units and found a weekly SP clinic to be a feasible model. Demand for the service may exceed available resources, highlighting the need for clear service criteria.
Rubin et al. 2005 (22)	*SP role*: Comprehensive admission assessment, including medical history, physical examination, medication review and communication with primary care providers. The SP developed health maintenance plans, addressed alcohol and tobacco risks, arranged vaccinations, participated in ward rounds, coordinated specialist referrals and supported post-discharge follow-up. *Effects of SP model*: Increased preventive health screening and improved continuity of care through collaboration with primary care physicians and follow-up after discharge. No significant impact on hospital charges or length of stay compared with usual care. *SP model feasibility*: Study demonstrated improved patient care with no overall difference in the cost of care.
Saik et al. 2007 (25)	*SP role*: Full responsibility for psychiatric inpatients' non-psychiatric medical treatment. *Staff experiences of SP model*: Psychiatrists and nurses overwhelmingly preferred the SP model to the previous model in which psychiatrists were responsible for non-psychiatric medical care. *Effects of SP model*: Citations for deficiencies in medical care by regulators were greatly reduced after the adoption of the model. *SP model feasibility*: Data suggests feasibility of SP service model, with potential benefits for quality of care and patient safety.
Behroozi et al. 2008 (27)	*SP role*: Assessment and treatment of common medical problems based on psychiatric staff referrals, with specialist referrals as needed and coordination of follow-up care after discharge through primary care providers. *Staff experiences of SP model*: Psychiatric staff reported satisfaction with SP consultations, daily ward involvement, continuity of care, and participation in patient management. *Effects of SP model*: The SP model reduced specialist referrals and supported collaboration between psychiatric and somatic services. Continuity of care was improved although patients lacking primary care providers remained an issue. The study highlighted ongoing service development and noted that employing GPs in hospitals may affect community GP availability, but also increase recognition of the value of GP services. *SP model feasibility*: Successful implementation of service with high staff satisfaction and observations of shorter length of stay and lower referral rates to specialists.
Goh et al. 2015 (23)	*SP role*: Comprehensive medical assessment on admission, including medical history, physical examination, somatic medication review. Management of new or ongoing physical health problems on the basis of referrals. *Effect of SP model*: Medical assessments increased significantly after implementation. While no clear changes in number of interventions or patient outcomes were found, the study asserts that the model improved management of physical comorbidities and allowed psychiatric staff to focus more on mental healthcare. Collaboration enhanced overall understanding of the needs of geropsychiatric patients. *SP model feasibility*: Achieved freeing up psychiatric staff time and enhanced interprofessional communication. *Other issues raised*: The study highlighted the need for more sensitive measures to evaluate service quality, awareness of comorbidities, outcomes at discharge, inter-specialist collaboration and post-discharge care.

Author, year	Key findings relating to the review
Tatreau et al 2016 (24)	*SP role*: Supervising a physician assistant for admission assessment of all patients and monitoring of patients with somatic comorbidities. Cardiometabolic issues were a significant concern. Facilitating primary care connection and appropriate prescriptions after hospitalization. *Effect of SP model*: Compared with usual care, the study found the model improved detection of hypertension, obesity, hyperlipidaemia, and tobacco use disorder. Patients with hypertension or hyperlipidaemia were more likely to receive appropriate medication at discharge, despite less laboratory testing. *Other issues raised*: Need to evaluate cost-effectiveness through measures such as treatment adherence, post-discharge care and rehospitalization. Proper documentation of chronic illnesses was considered valuable even when treatment was not initiated during hospitalization.
Mc Cracken et al. 2018 (28)	*SP role*: Consultation based on referrals from psychiatrists. Interpretation of laboratory results, clinical guidance, patient examinations and management of acute and chronic physical health problems. Common issues included musculoskeletal, dermatological, gastrointestinal, genitourinary, cardiovascular and respiratory conditions. SPs also coordinated with patients' primary care providers. *Effects of SP model*: Improved communication and continuity of care with primary care services, including follow-up after hospitalization. No effect on length of stay. Study suggests SP model may reduce unnecessary specialist referrals, overtreatment and costs. *SP model feasibility*: SP model is simple to replicate, providing a bridge between acute care and community family practice. *Other issues raised*: Lack of designated primary care providers threatened continuity of care. Further evaluation of cost-effectiveness, including rehospitalization rates, was recommended.
Wolsing et al. 2024 (20)	*SP role*: Somatic consultation in connection to the study, including evaluation and treatment of pre-existing and previously undiagnosed somatic health issues. *Patient experiences of SP model*: Patients valued access to physical healthcare during hospitalization. Interviews highlighted that psychiatric symptoms and treatment side effects could complicate somatic assessments, making timing and communication important. Collaboration between somatic and psychiatric staff was seen as essential for supporting ongoing care. *SP model feasibility*: Patients support SP model, but benefits depend on successful communication, timing of treatment and support of psychiatric staff.
Bloom-Feschbach et al. 2025 (21)	*SP role*: Reviewing new patient history, reviewing physical examinations conducted by nurses, providing consultation on acute and chronic disease management, medications and test results. Evaluation relating to ECT and ketamine treatment. Facilitating care transitions and continuity of care. Communication with patients' family members. *Staff experiences of SP model*: Psychiatrists valued SPs' medical expertise, communication and team-based approach. SPs found the role meaningful, particularly in identifying overlooked medical issues, opportunities for teamwork and learning and helping staff and patients navigate the healthcare system. Some challenges around role division and continuity were addressed through team discussions. *Effects of SP model*: Improved continuity of care, collaboration between psychiatric and medical staff, patient safety initiatives and quality improvement efforts. A partially remote service model supported service provision to multiple sites and enhanced SP work-life balance. The large SP team size influenced handoff continuity and team dynamics. Further research on cost-effectiveness and clinical outcomes was recommended. *SP model feasibility*: Model was feasible and helped address medical needs of psychiatric inpatients.
Mårtenson et al. 2025 (19)	*SP role*: Referral-based assessments and scheduled health checks addressing a wide range of physical health problems, particularly endocrine, cardiovascular, gastrointestinal, dermatological, musculoskeletal and genitourinary conditions. SPs also provided risk-factor screening, health promotion and specialist referrals when needed. *Effects of SP model*: SPs identified a variety of somatic conditions needing attention. SPs estimated their consultations to avoid a number of unnecessary referrals to emergency departments and somatic specialists. *SP model feasibility*: Model is a feasible solution to improve health of psychiatric inpatients and alleviate psychiatrists' workload. Great variety and prevalence of untreated diseases and somatic conditions identified by SP service, with treatment often time consuming.
Nissen et al. 2025 (30)	*SP role*: Somatic assessment in connection to the study, including health checks, screening, risk-factor management and health promotion. Key concerns included cardiovascular risk factors and vitamin D deficiency, with overall physical health found to be poor. *SP model feasibility*: Physical consultations should be routinely offered and adequate follow-up and support provided to ensure identified health problems are addressed. *Other issues raised*: The study recommended including a dedicated somatic health section in discharge summaries to improve communication with primary care.

Note: SP= somatic physician. ENT=ear, nose and throat, GP=general practitioner, ECT=electroconvulsive therapy

Table 3. Themes emerging in the included studies (n=12)

Themes	Key findings relating to the review
Context, resourcing and role of the SP	• mostly acute psychiatric wards in academic hospitals • visiting consultant or permanent member of the team, in one study remote supervisor of PA • from full-time to limited attendance at the wards • consultations, health examinations, screenings
SP responsibilities	• clinical summaries, medication reviews • evaluations of somatic issues • treatment of wide range of somatic illness (most common cardiovascular, gastrointestinal, musculoskeletal, dermatological, genitourinary and endocrine illnesses) • requesting referrals • health promotion • preventative tasks • assistance in navigating the healthcare system, including post-discharge care • education of the staff and patients
Staff and patient experiences of SP services	• psychiatric staff satisfied with consultations, better continuity of care, communication and teamwork, some challenges in delineating duties and from different expectations • SPs appreciated working with psychiatric inpatients and gaining expertise in a specific field • patients appreciated care, accessibility and quality of patient-doctor interaction in the SP service • patients need combined SP and psychiatric staff support due to SMI cognitive symptoms and side effects of psychiatric treatment
Systems-level changes	• improved rate of somatic diagnoses and treatment (but only 1 direct study) • better targeted specialist referrals • enhanced continuity of care • increased intra- and interprofessional collaboration • may energize further development in the quality of care • potential for improving regulatory compliance and patient safety (but only 1 study with limited evidence)
Economic aspects	• limited and inconclusive findings
Challenges in implementing the service	• psychiatric patients' need for support in care relationships • establishing role clarity and continuity of care during hospitalization • continuity of post-discharge care • resourcing the service • measuring impact

Note: SP=somatic physician, PA=physician assistant, SMI=severe mental illness

THEMES

Context, resourcing and role of the SP

SPs operated in a variety of inpatient contexts, which can be differentiated according to the patient population as well as in relation to the duration of the hospitalization. A number of studies were specifically concerned with either adult wards (20,27,28), psychogeriatric contexts (23,26) or a combination (28), with one study context also mentioning adolescents (25). One study noted that patients were of all ages , whereas many did not specify a particular age group (19,20,22,30). Four studies specified they were concerned with acute wards and short-stay areas (22,23,27,29), whereas in contrast the earliest study in the review came from a ward where the mean length of stay was 30 years (26). Three studies reported focusing on mostly patients with schizophrenia (24,26,29), and three on mostly patients with affective disorders (20,22,30).

The staffing and resourcing of the SP service were configured in various ways. Most common was a daily service, either on a part-time basis of 3-4 hours (19,23,27,28), or as a full-time service (22,25) on site or remotely (24). One study provided an example of a 24/7 service model (21). As an alternative to a

daily service, in one study the somatic service was configured as a weekly 3-hour session (29), and in another the SP visited the ward twice a week for an unspecified amount of time (26). Most typically the somatic service was provided by a single physician per facility (19,22,23,26,27,29), but in three studies the service was provided by a team of SPs (21,25,28). One study described a model involving a physician assistant on the ward, supervised by a SP (24). Instead of an established service model, two studies were concerned with arranged health evaluations conducted by visiting SPs (20,30).

Our analysis of the studies revealed different ways in which the SP role was configured. During the hospitalization period, most of the studies mentioned SPs acting as visiting consultants for psychiatric staff regarding the treatment of new or chronic somatic issues (19,26–29). Four studies specifically mentioned psychiatric doctors and nursing staff as the initiators of these consultations (19,27–29), with one of them also mentioning patients themselves as initiators (29). In three studies SPs were working at the wards, hence involvement in somatic issues was most probably requested without consultation, e.g. during daily hospital rounds (21–23). In one study, internists took full responsibility for the non-psychiatric medical care of inpatients (25). It is useful to appreciate that the role of the SP might be conceptualized in different terms, on a continuum from a visiting consultant to patients' attending somatic physician at the ward.

Responsibilities of the SP in the care process

Generating, reviewing and organizing information on patient health

Many of the studies noted how the SP service had improved the quantity, quality and organization of information relating to patients' somatic status. A central first step in achieving this was arranging medical assessments with SPs. These assessments were arranged in various ways, most commonly based on referrals by psychiatric staff or patient requests (19,21,27–29). In some settings, all admitted patients were offered an assessment on admission (23), a process which sometimes involved communicating with the patient's primary care provider as well (22). In one study the evaluation on admission was presumably carried out by a physician assistant supervised by the SP (24), and in another the SP would review the history of new patients and the results of physical examinations conducted by nurses (21). Information on patients' medical status could also be collected by scheduling examinations or health checks (19,26). Two studies were based on somatic assessments offered to inpatients in connection to the study (20,30).

Beyond their role in forming an initial picture of inpatients' somatic health based on assessment and review of medical history, SPs were noted as working to develop accessible summaries of physical health problems (26), reviewing medication (22,26) and drawing up plans relating to health maintenance (22). One study provided a detailed account of an SP working with a physician assistant to assign diagnoses for patients fulfilling criteria (24).

Diagnosis and treatment of somatic illness during hospitalization

SPs engaged in the diagnosis and treatment of a wide range of both acute and chronic somatic illnesses, although different categorizations of conditions in the studies complicated the analysis. Cardiovascular illnesses were reported as commonly addressed by SPs in the studies (19,24,26,28,29), as were musculoskeletal and dermatological conditions (19,26,28,29). Gastrointestinal (19,26) and genitourinary (19,28,29) conditions were also reported as a common issue of concern in multiple studies. Ear, nose and throat (26), respiratory (28) and endocrine issues (19) were reported as a common concern in single studies. In relation to chronic diseases, one study specifically mentioned poorly controlled hypertension and diabetes; this study also noted that the SP was engaged with diagnoses relating to critical health issues, such as a previously undiagnosed breast tumour and a severely anaemic patient requiring an emergency blood transfusion (29). Another study described several life-threatening cases with SP involvement (e.g. acute cardiovascular presentations) (21). One study mentioned the overprescription of somatic medication as a relatively common issue for the SP to encounter at the ward (26).

Health checks and health promotion

Studies also concerned the ways in which somatic physicians engaged in screening and interventions relating to risk factors and health promotion (19,20,22,26,29,30). This was achieved particularly through more or less comprehensive health checks conducted by the SP (19,20,22,26,30). In studies where details were given, two studies mentioned that a comprehensive medical history was obtained from the patients, and the physician conducted a physical examination (22,26). Another study mentioned blood tests, measurement of vital signs and the use of a health questionnaire (30).

Cardiovascular risk factors, especially smoking, were specific concerns in several studies (22,24,26,30). Two studies mentioned the role of the SP in nicotine replacement therapy (22,24). One study gave a detailed account of the somatic physicians' health promotion activities, including drawing up

alcohol and smoking cessation plans, lipid screening, organizing the collection of stool cards, mammograms, pap tests, prostate examinations and arranging for vaccinations (22). Elevated BMI was mentioned in two studies (24,30), and vitamin D deficiency in one (30). Health promotion could involve educating patients on their specific illnesses, such as the management of diabetes, as well as addressing patients' anxieties relating to somatic health and advising them on exercise (29).

Coordination and the continuity of care

Finally, some of the studies pointed to the role of the SP in coordinating communication and the continuity of care. This involved both onward referrals to specialists as needed (19,22,26,27), and communicating with the patients' primary care provider during the hospitalization period (22,24,28). One study mentioned communication with the patients' family members (21). Additionally, SPs were involved in facilitating follow-up care after discharge (27), which might necessitate further communication with the patients' primary care provider (22,24). In one case, the physician supervising the somatic team on the wards also provided outpatient primary care in the same facility, providing a primary care contact for patients discharged without a primary care physician (24).

Staff and patient experiences of SP services

Staff experiences: satisfaction, teamwork and points of friction

Three of the studies were concerned with staff experiences related to a SP service in psychiatric inpatient settings (21,25,27). Behroozi reported psychiatric ward staff respondents to a survey as being highly satisfied with the timeliness and appropriateness of consultations, provided by the SP on daily visits to the wards (27). Staff respondents were also highly satisfied with the continuity of care in relation to the service. A lesser but still notable proportion of respondents were very satisfied with the SP's communication and involvement of staff related to patient management plans (27).

Saik investigated the experiences of psychiatrists and nursing staff regarding the implementation of an SP model where internists took full responsibility for the non-psychiatric medical care of psychiatric inpatients, finding overwhelmingly positive experiences among both groups (25). Psychiatrists preferred this model because it reduced their concerns of missing serious medical problems, allowed them to focus on psychiatric issues and reduced their feeling of exposure to legal risks. They described their working relationship with the SPs as excellent or good. Nurses felt more comfortable with SPs addressing medical issues, and found it simpler to contact the physician tasked with addressing the problem in the SP model (25).

Bloom-Feshbach examined in detail the experiences of both psychiatric staff and SPs themselves in relation to a 24/7 somatic physician service provided to a psychiatric hospital by a team of hospitalists, finding a variety of positive experiences reported by both psychiatrists and SPs (21). They reported that psychiatrists valued not only the medical expertise provided by the SPs, but also their proactive communication and the possibility of engaging in team-based problem solving. The authors reported SPs as taking pride and finding meaning in their work role, particularly in relation to attending in detail to medical problems which might have otherwise been missed. SPs saw their role not only as contributing expertise in clinical medicine, but also helping both patients and psychiatrists in navigating the health system to meet the, often complex, needs of psychiatric inpatients. SPs valued the way in which the role allowed them to expand the scope of their practice, allowing them to learn from their psychiatric colleagues and gain clinical experience in a new setting. They also valued the work-life balance and support for family life afforded by the hybrid SP work in psychiatry, particularly in relation to opportunities to work fewer weekends, more day shifts and the ability to work remotely. Both psychiatrists and SPs valued opportunities for teamwork and found meaning in caring for a vulnerable patient population (21).

Bloom-Feshbach also noted points of friction in interdisciplinary teamwork. In the implementation of the new hybrid model with several SPs, frequent handoffs between the team of SPs could negatively impact continuity with patients and teams. The high level of medical support led some psychiatrists to feel uncertain of the division of duties between psychiatrists and SPs. Psychiatrists and SPs had different expectations in some areas of care, such as the adequate patient history and physical examination on admission. Furthermore, in their setting, nurse practitioners were required to be supervised by physicians, and the division of this responsibility was another potential source of friction. SPs sought to mitigate these issues by engaging in discussions with nurses and psychiatrists to determine issues of anticipated length of stay, the scope of medical issues to pursue during the admission period and outpatient follow-up (21).

Patients' experiences: accessibility, trust and the need for ongoing support

Welthagen interviewed patients seen by the SP during their inpatient stay, finding very positive experiences (29). All the interviewed patients were satisfied with the care provided

by the SP, whom they described as professional, kind and understanding. Most of the patients seen by the SP also felt that their physical needs were taken seriously by their psychiatric teams. Half of the patients stated that they preferred to see the SP rather than their own general practitioner during their hospitalization, due to ease of access and easy communication between the SP and ward psychiatrists. Some patients nevertheless preferred to see their own GP, due to their greater familiarity with the patients' health. Regarding improvements to the SP service, some patients suggested a greater number of weekly clinics and better information regarding access to the service for new patients (29).

Wolsing interviewed hospitalized psychiatric patients who had received a health examination by the SP (20). Similar to Welthagen, they found that patients held a mostly positive attitude to the service, with many of them perceiving advantages of the appointment relating to issues such as evaluating and treating pre-existing medical conditions and confirming the absence of somatic disease. The interviews revealed how patients' acute psychiatric symptoms during psychiatric treatment need to be considered in the timing of health checks. Memory impairment made recollecting the medical consultation difficult for many of the patients. The interviews highlighted the importance of the patient-doctor relationship for patients' experiences, with the doctors' attentiveness, empathetic listening and prior preparation relating to understanding the patients' situation emerging as significant. Patients expressed a wish for support from staff in initiating somatic assessments and treatment by the SP, as well as broader support in relation to issues such as physiotherapy, dietary consultations and smoking cessation. The interviews also pointed to patients' dependence on staff proactivity in sustaining the continuity of somatic treatment (20).

One further study included a short note according to which the SP service was valued by patients, who were able to develop trust in the physician, which allowed for procedures such as intimate physical examinations (26). This was in contrast to a prior model in which somatic care was entrusted to junior doctors on six-month assignments.

Systems-level changes

Improving rates of diagnosis and treatment

Three of the studies were concerned with comparisons between an implemented SP model and usual treatment (22–24). One of these studies concerned a service model where a physician assistant was supervised by the SP, demonstrating the achievement of higher rates of diagnosis for patients fulfilling criteria for diagnoses of hypertension, obesity, hyperlipidaemia and tobacco use disorder (24). On discharge, patients in the intervention group diagnosed with hypertension or hyperlipidaemia were more commonly on appropriate medication, suggesting the information collected by the SP and their assistant was used in adopting appropriate medical treatment (24). Another study did not concern diagnoses, but showed how the implementation of the SP model led to lipid screening, stool card collection, mammograms, pap tests and prostate examinations, all of which were practically missing before the implementation of the model (22). One study was concerned with the number of various medical interventions as well as patient outcomes prior to and after the implementation of the SP service (23). This study found practically no difference in interventions and outcomes, but the authors propose that this may be due to insufficiently sensitive indicators (23).

Better targeted specialist referrals

Three of the studies proposed that the SP service might avoid unnecessary referrals to specialist services (19,27,28), with one of these connecting this to a potential reduction of overtreatment and care costs (28). One of these studies demonstrated a decreased rate of referrals to specialists after the initiation of the SP service, noting also that referrals by the SP might be more appropriate than those by psychiatric staff, thus improving the overall use of specialist services (27).

Continuity of care

Many of the studies were concerned with efforts to improve the continuity of care between the psychiatric wards and primary care. SPs' efforts in communicating with primary care providers were cited as improving the continuity of care through better follow-up of medical issues identified during hospitalization (22,24,27,28). One study asserted that the treatment of physical comorbidities in the hospital ward was achieved with no loss in the continuity of care (23). Maintaining a list of patients with attached summaries and task lists was noted as a measure for enhancing continuity of care (21). SPs were also noted as taking an active role in navigating the health system, particularly in relation to emergency services and general hospital physicians (21). In the case of long-stay inpatients, one study noted that the distance to primary care can only be remedied by dedicating the resources of a primary care specialist to this patient group (26).

Increased intra- and interprofessional collaboration

Some of the studies examined ways in which the implementation of a SP service led to increased intra- and interprofessional collaboration. One study mentioned the education provided by SPs to psychiatric staff in relation to specific patients and their medical conditions (29). Another study related practical experiences of the somatic service, noting that psychiatric staff had been better able to focus on psychiatry after the implementation of the service, although these observations were not based on a systematic analysis (23).

Several of the studies noted how the practical work of implementing a SP service had helped to create new infrastructure and catalyse a culture of collaboration between somatic and mental health practitioners, with ongoing learning between somatic and psychiatric staff (21,23,27). In one study, the somatic service was described as reorienting geropsychiatric staff to develop a more comprehensive understanding of patients' somatic needs, with the team engaging in discussions which had heightened awareness of medical interventions in relation to dementia patients and types of the more frequently necessary interventions (23). More collaborative cultures were described as holding potential for the practitioner-driven development of further initiatives, such as shared care models in the community (27), as well as scholarly collaboration (21).

Job quality and staff retention

One US study noted physician burnout to be prevalent in general internal medicine (21). In this context, the study noted that a SP service for psychiatric inpatients utilizing virtual medicine can provide a more sustainable job quality for SPs, allowing for work-life balance and improving the meaningfulness of work through opportunities for interprofessional communication and involvement of the patients' family in care. This in turn can benefit the retention of SPs in psychiatric services (21).

Regulatory compliance and patient safety

One study compared the amount of citations by regulators related to deficiencies in medical care at the studied hospital, finding the amount of these citations to have fallen from 10 to one when comparing periods before and after the implementation of the SP service model (25).

Further improvement, formalization and expansion

Some of the studies involving newly implemented SP services noted how experiences of these services had sparked further improvement efforts. SPs were described as involved in new initiatives relating to patient safety, quality improvement and electronic medical record optimization in the mental health settings (21). In a psychogeriatric context, the experience of utilizing a SP was reported as enabling the consultant geriatrician to be present on ward rounds, while links between psychogeriatric and geriatric care were strengthened (23). One issue is developing ways to measure the effects of newly implemented services, which can involve measuring medical outcomes at discharge, inter-specialist collaboration and/or post-discharge care (23).

Some of the studies noted efforts toward formalization and expansion of the SP service, such as in the formalization of a somatic consultation service so that it might be offered to more departments (27), or in the collaborative creation of new clinical guidelines, such as those relating to obesity medication prescriptions (21). The study by Bloom-Feschbach noted that the implementation of the service in a virtual mode held potential for its expansion into multiple sites across the psychiatry line, which would also support the standardization of the medical protocols of the service (21). In addition, one study reported collaboration with the emergency department to connect patients without primary care physicians with these contacts (27).

Economic aspects

Two studies in the review examined the costs of the SP service (22,24). Rubin found no difference in patients' hospital charges between the usual care group and the SP group (22). The other study described an SP service where less laboratory tests were taken compared to treatment as usual, while nevertheless achieving simultaneous higher rates of treatment for hypertension and hyperlipidaemia, interpreting this outcome as a cost saving (24).

In evaluating effects of the SP service on patients' length of stay at the hospital, one study showed a decrease of length of stay during the study period, however, the author reasoned that the effect was probably not solely attributed to SP services (27). Two other studies found no difference (22,28).

Challenges in implementing the service

The studies uncovered a variety of both potential and practically encountered issues worth considering in the implementation of SP services for psychiatric inpatients.

Supporting psychiatric patients in care relationships

As previously noted, one study provided significant in-depth information on psychiatric inpatients' experiences of medical assessments by an SP during their hospitalization (20). Psychiatric inpatients often experienced memory and cognitive problems complicating the treatment of their somatic issues. Attaining trust between SPs and patients was noted as dependent on the quality of interaction in patient-doctor relationship. Additionally, the support of psychiatric staff emerged as highly important in initiating and following up on somatic assessments, including a preparedness to coordinate the timing of psychiatric and somatic treatment (20).

Continuity and role clarity during hospitalization

One of the studies provided details of challenges in implementation related to continuity and role clarity (21). In the case of a team of SPs providing the service, the impact of the frequency of patient handoffs between these SPs needs to be considered, and the size of the team has an impact on team dynamics. Virtual medicine can be employed in establishing the SP service, but this entails recognizing its limitations, which can be mitigated by a hybrid model with collaboration between on-site and virtual clinicians. Role clarity between specializations and professions needs to be established, necessitating ongoing discussion between psychiatric staff and SPs, as well as between physicians and nurses, in order to avoid problems such as medication reorders and missed lab results. This involves practical work such as establishing shared conceptions for proper procedures regarding patient history and examination on admission (21).

Continuity of post-discharge care

The post-discharge connection to primary care was noted as a problematic point in two of the studies, with patients' lack of designated primary care providers jeopardizing the continuity of care (27,28). One study recommended the dedication of a section in the epicrisis to the somatic status of the patient to improve handovers from hospitals to primary care (30).

Resourcing

The resourcing of the SP service is potentially more feasible when patients with physical comorbidities are concentrated, and less so in contexts where patients with fewer physical health problems are dispersed in small units (26). When the service is implemented, demand may exceed resources, requiring the adoption of service criteria, disappointing some patients (29). Particular contexts may present a great variety and amount of untreated diseases and somatic conditions, treatment of which may be time consuming even for SPs (19). Finally, if GPs are in short supply, utilizing them in hospitals may have an impact on community services, although this may also serve to improve recognition of the value of skilled generalists (27).

Measuring impact

Several of the studies noted a need for more information regarding the measured effects of the implemented SP service models (21,23,24,28). A variety of potential measurements relating to different points in care processes were proposed in the studies.

In relation to the hospitalization period, one study proposed prospective studies measuring length of stay, transfers to local emergency departments and number of patients sent out for examinations, as well as clinical metrics such as diabetic and blood pressure control (21). Another study noted that rare events such as emergency medical transfers may not function as sufficiently sensitive indicators of the effects of the SP service (23). This study proposed measuring medical outcomes at discharge, as well as inter-specialist collaboration, such as increased communication between disciplines and increased awareness of comorbidities (23).

Beyond discharge, some of the studies proposed measuring post-discharge care (23,24). The rate of rehospitalization was noted as an interesting measure in multiple studies (21,24,28). Some studies noted the overall importance of developing an informed understanding of the potential cost savings and cost-effectiveness of SP services for psychiatric inpatients (24,28).

DISCUSSION

Since the previous review examining SPs within psychiatric inpatient context from 2010, the topic has gained some interest, e.g. four publications in 2020s, indicating the relevance of this study field. Over the past thirty years, major changes in the care of individuals with SMI have taken place, including deinstitutionalization, task shifting of SMI outpatient care from psychiatrists to GPs and the introduction of second-generation antipsychotics. Despite these developments, the studies in our review highlight persistent challenges regarding somatic health and care of patients with SMI over four decades: multimorbidity, under-resourcing of services, difficulties in accessing primary care, discontinuities between secondary and primary care and the importance of improving service quality.

Range of SP service models

This review identified a range of models for integrating SP services into psychiatric inpatient settings. These ranged from full-time, even 24/7 availability, to limited attendance via electronic medical record contacts and phone calls (19,21). The most common model was SPs consulting inpatients' somatic concerns, although health examinations and screenings were common SP activities as well. In one study, the SP remotely supervised a physician assistant (24). The variability of service models reflects a variability of care settings in different healthcare systems.

SP role in care

SPs were shown to execute numerous tasks contributing to the evaluation, treatment and prevention of somatic illness, as well as improving continuity of care. SPs also generated clinical summaries, reviewed medications, facilitated referrals and assisted both patients and psychiatric staff in navigating the healthcare system. Continuity with primary care is an area in which SPs have contributed, even though potential for improvement seems to remain (27,28).

Most studies in this review assessed the spectrum of somatic illnesses encountered in consultations and health checks by SPs. The range of somatic problems encountered was wide, and diagnoses fell predominantly in the category of general practice, aligning with the extensive literature on somatic comorbidity in SMI (4,31). The somatic care of psychiatric inpatients is complicated by both SMI itself as well as the process and effects of psychiatric treatment (20). This places great demands on physicians entrusted with managing and coordinating psychiatric inpatients' somatic care.

Psychiatrists have been encouraged to take responsibility of the somatic care of their patients (32,33), but this can be impractical, as they often lack opportunities for maintaining up-to-date general medical skills. A lack of appropriate equipment and infrastructure forms one constraint (11,26), as does time pressure relating to a shortage of psychiatrists (32). Gathering information from medical records, examining patients, diagnosing and treating somatic illnesses and coordinating care pathways towards primary care are demanding and time-consuming tasks even for experienced GPs (19). Younger doctors specializing in psychiatry have typically been relied upon in somatic issues emerging in psychiatric wards (10). In Finland, doctors specializing in general practice and rotating irregularly for a couple of months in psychiatry have been a valuable resource in the services. However, lack of continuity and difficulties in engaging in long-term quality improvement is problematic in this kind of task allocation.

Experiences of SP services

In studies evaluating experiences, both staff and patients appreciated SPs for their medical expertise and for the support they offered in patient care. Effective collaboration between psychiatric and somatic staff was seen as essential, particularly in managing fluctuating psychiatric states, coordinating psychiatric and somatic treatments and ensuring follow-up when patients themselves lack the capacity to do so (20). Staff also appreciated new opportunities for teamwork and shared learning (21,23,27), whereas SPs themselves reported satisfaction derived from working with vulnerable patients and gaining special expertise (21). Distributing the workload of caring for psychiatric inpatients between psychiatrists and SPs may help create space for patient-doctor relationships founded on communication, trust and familiarity with the patients' situation.

Different contexts of SP service

Most studies in this review focused on acute psychiatric wards. Nevertheless, the need for somatic care is evident also in the case of long term-psychiatric inpatients, nowadays typically in forensic units. Interestingly, only two studies in this review reported activities from forensic units (19,25). In the UK, the availability of GPs in forensic units has been established, at least to some extent (34). The wide work fields of SPs and the high level of satisfaction reported by both patients and the staff suggest that the burden of somatic problems requiring attention is substantial in both acute and long-term psychiatric inpatient care.

Residing in a general hospital campus bears a promise of flexible collaboration with other medical specialties, the availability of a hospital's medical emergency team and 24/7 diagnostic services. Interestingly, both Canadian studies were conducted in such an environment and reported high contentment of the SP service and improvement/decrease in referrals to medical specialties (27,28). This suggests that somatic (sub) specialty consultants in general hospitals can be distant from the daily practice in psychiatry, including roles such as education and patient safety/quality improvement. In contrast to dedicated SPs, somatic (sub)specialists would also lack opportunities to deepen their expertise in relation to psychiatric patients (21). They would also be missing the wide spectrum skillset of a GP.

Implementing and developing new services

Introducing SP services requires careful design, including clear delineation of roles and responsibilities. However, the reviewed studies emphasize implementation as an ongoing, interprofessional process (see also 35,36). As practical issues emerge, ongoing discussion is necessary in developing the service, tackling emerging issues and mitigating frictions (21). This process can in itself foster a collaborative culture of care between different professionals, which in turn serves to mitigate implementation issues and to drive further development (21,23,27). In the phase of establishing permanent SP services within psychiatric settings, formulating and reassessing policies and protocols accordingly is worthwhile.

User involvement is critical in shaping services, although engaging psychiatric inpatients in research remains challenging due to symptom severity, consent processes and resource constraints. Forensic and involuntary patients may be particularly difficult to include in study groups (20,30). In addition, limited participation rate in the most recent Danish study highlights the need for improved strategies in enrolling participants (30).

Economy and effectiveness

In the light of constraints on healthcare resources, demonstrating cost-effectiveness for new initiatives appears increasingly important. While hospitalist models in somatic inpatient care suggest potential benefits such as reduced length of stay and unnecessary testing (37,38), these outcomes are difficult to capture in small-scale studies of SP services. Developing sensitive indicators for patient outcomes is a challenge (23). One possibility could be to evaluate opportunity costs by "time savings", as SP involvement can free psychiatrists' time and enable more efficient use of specialist referrals. As shown by Mårtensson (19), two-thirds of SPs' patient assessments took longer than half an hour, demonstrating the time-intensiveness of somatic care.

Possible drawbacks of the SP model should be considered. Concerns about narrowing psychiatrists' clinical scope appear less relevant given the shortage of SPs in psychiatric services. Another concern is the possibility of increased somatic investigations by SPs leading to somatic overtreatment and inappropriate resource allocation from psychiatry to somatic care.

STRENGTHS AND WEAKNESSES IN THE REVIEW

The primary strength in our review is in developing a comprehensive overview of the research themes identified in the diverse and scattered studies on SPs in psychiatric inpatient services. The most recent review we identified dates to 2010 and provides only a limited descriptive analysis of its findings (17). In addition to executing a thematic analysis, we were able to include four recent publications from 2020s (19–21,30). Revealing the scarcity in this research field by being able to identify only twelve papers over the past thirty years is a significant finding in itself.

A flexible search strategy incorporating multiple literature retrieval methods allowed us to identify, to the best of our knowledge, the available empirical studies published over the past four decades, across diverse psychiatric inpatient settings and healthcare systems, despite substantial variation in research methodologies and terminological usage.

However, heterogeneity and a limited number of typically small-scale studies, executed often in pilot phases of the service and in diverse health care systems prevent the creation of an exhaustive picture of the phenomenon and can surely be considered as weaknesses. In addition, the large time span in the identified articles downgrades the contemporariness of this review.

Regarding weaknesses, the absence of findings regarding direct, individual patient-reported health outcome measures is evident. In addition, it is plausible that included studies were able to show just a narrow view of the SP activities and effects in the healthcare ecosystem, leaving probably meaningful tasks of improving the quality of care, patient safety and work flows unreported and unpublished.

In generalizing the findings of our review, caveats especially related to features in healthcare systems need to be considered. Half of the included studies came from North America and Australia, with diverse healthcare systems compared to Europe. Especially in the US, financing/billing structures, professional roles (e.g. hospitalist, physician assistant) and mandatory procedures (e.g. before neuromodulation therapy and on hospital admission) differ from European ones. In addition, the role of GP and patients' attachment to her/him differs even across Europe. For instance, in some countries primary care GPs are sometimes involved in the treatment of her/his patient during the hospitalization (39).

FUTURE DIRECTIONS IN RESEARCH

Several phenomena occur simultaneously in and outside healthcare settings where the effects of an intervention ought to be studied, leading to difficulties in evaluating the effects of a single piece in the puzzle. However, in considering new healthcare services, scientific foundations are mandatory and consequently, the justification to study this topic further is evident.

Measuring the effects of SP involvement for inpatients' somatic illnesses and risk factors is a challenging exercise, but could be possible in large scale, permanent settings established over long time frames. In addition to outcomes regarding patients' health and wellbeing, nuanced evaluation of multiprofessional collaboration, including hidden work and effects that arise from the embedded presence of a SP in psychiatric services, is fundamental in order to understand and foster probable positive effects on patient care and work wellbeing. The importance of research of user experience in relation to feasibility and communication can't be overestimated.

Somatic patient safety in psychiatric inpatient settings is surprisingly under-researched, e.g. only infection prevention has gained minimal interest so far (40). Examining SPs´ roles and impact in patient safety outcomes is a meaningful direction in research as well.

To our knowledge, permanent SP models in psychiatric inpatient settings exist sporadically (14,39,41,42). Descriptions of these "hot spots", and of possible "hidden gems" as well, especially concerning the formation phase and resourcing, would be beneficial.

All except for two (26,29) studies in this review were made at university hospitals, presumably reflecting scientific infrastructure, know-how and incentives available in academic environments. Interestingly, the majority of the first authors of the included studies were non-psychiatrists. The study of SPs in psychiatry necessitates the involvement of services users, SPs themselves and collaboration between medical and other academic disciplines.

IMPLICATIONS

The amount of high-quality research and guidelines produced over the decades on somatic comorbidity in SMI is overwhelming, but modifications in psychiatric services to address this Gordian knot remain few. Hence, both users of the psychiatric services and their carers, as well as clinicians and administrators, have suggested engaging somatic expertise within mental health settings in order to diminish health disparities in individuals with SMI (12,43). The Lancet Psychiatry Physical Health Commission recently called for more efforts in psychiatric settings to deliver holistic care: effective and feasible lifestyle interventions and prevention/management of psychotropic medication side effects (44,45). Health examinations and screenings for medication side effects and risk behaviours make needs for preventative interventions visible. Typical obstacles for implementation of holistic care, such as shortage of resources, lack of training and unclear roles and responsibilities highlighted by the Commission, could be alleviated to some extent by the involvement of SPs.

Reflecting the findings of this review, and national/international experiences (34,39,42), it seems that GPs may have the most suitable skillset for the task of fostering somatic services and systems-level improvement in psychiatric inpatient settings. Management of various acute and chronic, often complex somatic problems, as well as prevention of diseases and health promotion are the core competencies of a GP (46). GPs are often aware of primary and secondary care pathways and able to ease transitions between secondary and primary care as well. In addition, collaborating with citizens and healthcare partners from different backgrounds is familiar for GPs metaphorically "speaking several languages".

Ultimately, several possible models exist in bringing SPs to psychiatric inpatient settings for the best of patients and the staff. The implementation of such models needs to consider differences in contexts of care and national healthcare systems. In our review, establishing ongoing interprofessional dialogue in a collaborative culture of care quality improvement emerges as the key to developing SP services tailored to the needs of psychiatric inpatients.

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Use of generative AI in the article process: AI-assisted search term creation has been described in the methods section. Additionally, Microsoft Copilot was used to support the summarization process for the Abstract, and to streamline language and reduce word count of the manuscript.

Supplementary Material

Supplementary data are available at Psychiatria Fennica online.

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PHARMACOGENETIC PANEL TESTING IN SPECIALIZED PSYCHIATRIC CARE - PILOT STUDY

ABSTRACT

Background: *Psychiatric medication response and adverse effects show substantial interindividual variability, partly due to genetic differences in drug metabolizing enzymes, which pharmacogenetics seeks to address to optimize treatment. Although its clinical use has expanded in psychiatry and may improve outcomes and cost-effectiveness, less is known about patient selection and real-world implementation. This pilot study describes pharmacogenetic panel testing in specialized psychiatric care, focusing on patient selection, underlying clinical factors and the testing process timeline.* ***Methods:*** *The study included participants from Oulu University Hospital specialized psychiatric care with individuals identified via the Nordlab laboratory information system. Data was collected manually from the ESKO electronic health record system for participants over 13 years of age who were tested between 1 January and 30 June 2024. Data extracted from patient records included clinical, demographic and testing-related variables.* ***Results:*** *The study included 133 participants who underwent pharmacogenetic panel testing (mean age 32.2 years). The most common diagnoses were unipolar depression (35%) and psychosis (27%). On average, participants had tried 1.33 antidepressants and 1.29 antipsychotics before testing, with antipsychotics being the most used medication group at the time of testing. The main indications for testing were medication optimization, and poor response or adverse effects, however, the indication was not documented in 21% of referrals. The mean time from referral to result availability was 24.8 days and to analysis completion 59.8 days.* ***Conclusions:*** *Pharmacogenetic panel testing appears to be primarily targeted toward general medication optimization and difficult-to-treat psychiatric patients, although the clinical utilization and documentation of test results remain variable. The findings support the need for clearer clinical processes and standardized documentation practices to facilitate the integration of pharmacogenetics into psychiatric care.*

KEYWORDS: PSYCHIATRIC, PHARMACOGENETIC, PANEL, TEST, SPECIALIZED PSYCHIATRIC CARE

INTRODUCTION

There is substantial interindividual variability in the response to psychiatric medications and in the occurrence of adverse effects (1). In clinical practice, patients often undergo multiple medication trials before an effective drug and appropriate dosage are identified. In antidepressant treatment, complete symptom remission is achieved in only approximately 40% of patients (2). Clinical response to first-line antipsychotic treatment is achieved in approximately 60–70% of patients (3).

The process of identifying effective psychiatric medication may be prolonged and place additional strain on both patients and the healthcare system. Interindividual differences in drug response are partly explained by genetic variation in enzymes involved in drug metabolism (4). To identify these genetic variations and to support individualized medication treatment, pharmacogenetics is utilized (5). Pharmacogenetics enables the prediction of drug responses, reduction of the risk of adverse effects and optimization of treatment efficacy. Clinical pharmacogenetics is grounded in research on gene structure, genotyping and genotype–phenotype associations (6). The use of pharmacogenetics in clinical practice has increased in recent years, and its application has expanded to psychiatry. Evidence suggests that pre-emptive genotyping may improve treatment outcomes and cost-effectiveness (7,8). Cost savings arise particularly from a reduction in adverse effects, decreased need for hospitalization and faster achievement of effective treatment (8). The patients who appear to benefit most from testing are those who have had an inadequate response to medication or who experience clinically significant adverse effects (9,10).

Although the clinical utility of pharmacogenetics has been increasingly studied, research has primarily focused on evaluating clinical effectiveness and implementation in healthcare settings (11). In the context of psychiatry, research has mainly concentrated on individual genes and specific drug classes, particularly cytochrome P450 enzymes, CYP2D6 and CYP2C19 enzymes and antidepressant medications (12). In addition, studies have examined the association between these genetic variants and antidepressant response across multiple clinical cohorts (11). Less attention has been given to the practical implementation of pharmacogenetic testing (PGx) in psychiatric clinical practice, including patient selection for testing, clinical indications for testing and the use of results in treatment decision-making (6,11). Systematic evaluation of these processes in psychiatric specialized healthcare remains relatively limited.

The aim of this registry-based pilot study was to describe the PGx testing process in psychiatric specialized healthcare. The study examined which patients and patient groups were referred for PGx testing and the factors leading to such evaluations. In addition, the time required for the PGx testing process from test request to the completion of results and analysis was assessed. The primary research question was: "How is PGx testing implemented in specialized psychiatric care?" The sub-questions are: "Which patient groups were tested, including their sociodemographic characteristics, and why?" and "How much time elapsed from the test request to the completion of results and subsequent analysis?"

MATERIAL AND METHODS

DATA

The pilot study was conducted at the Department of Psychiatry, Oulu University Hospital (OYS Psychiatry). The study population consisted of patients 13 years and older who were treated in OYS Psychiatry, for whom PGx panel testing had been performed between 1st January 2024 and 30th June 2024. OYS Psychiatry consists of psychiatric inpatient wards within a university hospital, adolescent and adult psychiatric outpatient units, the psychiatric emergency unit and regional psychiatric units of Oulaskangas (inpatient ward and outpatient services). Data collection was based on patient identifiers obtained from the Nordlab laboratory information system. The data were collected manually from the ESKO electronic health record system. A total of 133 patients were included in the study, and the only exclusion criteria was age under 13 years.

The data collected from the patient record system are presented in *Table 1*. The data were compiled into a single Excel file for further analysis. Information extracted included the patient's primary psychiatric diagnoses, gender, age at the time of PGx testing and age at disease onset. Data on the patient's psychiatric medication history prior to testing, as well as the current medication list at the time of testing, were also collected. In addition, the indications for PGx testing were recorded, as well as the unit from where the referral to the PGx testing was done. Dates related to the testing process were extracted, including the date of test referral, the date of result availability and the date of completion of the analysis. Furthermore, information on who performed the analysis (pharmacist or physician) was collected. Analysis refers to the process in which the treating physician or pharmacist reviews the patient's medication in relation to the test results and documents the findings in the patient's health record. Finally, it was documented whether and how the PGx test results were mentioned in treatment planning. This was intended to also capture patients for whom no formal analysis had been performed.

STATISTICAL ANALYSES

The statistical analysis of the data was performed using IBM SPSS Statistics software. For continuous variables, the mean and standard deviation (SD) were calculated. These were used to describe age (at the time of PGx testing and age at disease onset), the number of previous psychiatric medication trials and time in the PGx testing process.

For categorical variables, cross-tabulation analysis was performed, and frequencies and percentages were reported. This method was used to analyse indications for PGx testing, current medications at the time of testing, diagnoses, unit from where the referral to PGx testing was done and documentation in patient records.

ETHICAL CONSIDERATIONS

Research permission was obtained from the Wellbeing Services County of North Ostrobothnia (Pohde), along with a data permit (TIEL:32/2025, TUTK:234/2025). In addition, a separate research permit was obtained from Nordlab for the release of personal data. The study was conducted in accordance with the guidelines of the Finnish National Board on Research Integrity (TENK 2023). As the study was a registry-based study, approval from an ethics committee was not required.

Table 1. Data collected from the patient health records

Data	Description
age	age of onset of the psychiatric disorder and age at time of PGx test
gender	male/female
primary psychiatric diagnoses	primary psychiatric diagnosis at the time of referral to PGx test
medication treatments	previous psychiatric medication treatments before PGx testing and at the time of PGx testing
other therapeutic interventions	exposure to ECT, TMS or ketamine treatment
indication/indications for PGx testing	medication optimization, adverse drug reaction, non-response to medication, testing process initiated by the patient
dates of assessment	PGx test request date, sample collection date, result date, analysis completion date
performer of analysis	pharmacist/ physician
clinical documentation	Was the PGx test result documented in the patient record or considered in patient care?

(PGx=Pharmacogenetic, ECT=Electroconvulsive Therapy, TMS=Transcranial Magnetic Stimulation)

RESULTS

SAMPLE

The study sample consisted of 133 individuals (mean age 32.2 years) who underwent PGx testing between 1 January and 30 June 2024. The analyses included test panels 11611 B-Farm-D and 11849 B-PGx-D (*Table 2*). On average, the participants had tried 1.33 (SD=1.48) antidepressants and 1.29 (SD=1.27) antipsychotics prior to PGx testing. The most common primary psychiatric diagnostic groups were unipolar depression 35% (n=46) and psychosis 27% (n=36). Most referrals originated from psychiatric inpatient wards within a university hospital (n=55, 41.4%) and from adolescent and adult psychiatric outpatient care (n=41, 30.8%).

INDICATIONS FOR PGX TESTING, TIME FRAMES AND DOCUMENTATION PROCEDURES

The most common indication for conducting the PGx test was optimization of medication (n=56, 42%) (*Table 3*). Medication optimization refers to all entries in the patient records where the physician indicated that the PGx test was ordered to support treatment planning. Other common indications for conducting the PGx testing were adverse drug effects or poor response to medication. Indication was missing information in one fifth (n=28, 21%) of the PGx test referrals. Polypharmacy was not mentioned as indication for PGx for any of the subjects.

In the study cohort, 52% had their PGx test result recorded in the patient records (*Table 4*). More detailed result analysis had been conducted for 18% of the participants. The average time from referral to the panel to completion of the analysis was 59.8 days (SD=64.6). The average time from referral to ordering the panel and receiving the results was 24.8 days (SD=18.2).

Table 2. Background characteristics of the study population

	Total (n=133)
Background variable	
Female (n, (%))	86 (64.7)
Age (mean, (SD))	32.2 (15.2)
Number of antidepressants before PGx test (mean, (SD))	1.33 (1.476)
Number of antipsychotics before PGx test (mean, (SD))	1.29 (1.265)
Onset age of the psychiatric disorder (mean, (SD))	23.53 (13.06)
Main diagnosis	**n (%)**
Unipolar depression	46 (34.6)
Psychosis	36 (27.1)
Other[1]	33 (24.6)
Anxiety disorder	11 (8.3)
Bipolar disorder	7 (5.3)
Psychiatric medication at the time of PGx test	**n (%)**
Antipsychotic	95 (71.4)
Antidepressant	69 (51.9)
Mood stabilizer (including lithium)	14 (10.5)
Sedatives	33 (24.8)
PGx test referral location	**n (%)**
psychiatric inpatient wards within a university hospital	55 (41.4)
adolescent and adult psychiatric outpatient units	41 (30.8)
psychiatric emergency services	23 (17.3)
psychiatric inpatient ward of a regional hospital	7 (5.3)
outpatient care units of a regional hospital	7 (5.3)

(SD=Standard Deviation, PGx=Pharmacogenetic)
[1] Other most commonly refers to obsessive-compulsive disorders and eating disorders. None of the subjects had substance use disorders as main diagnosis

Table 3. Indications for PGx testing

Indication for PGx test	total n=133, n (%)
Medication optimization	56 (42.1)
Indication not documented	28 (21.1)
Adverse drug reactions (ADRs)	26 (19.5)
Non-response to medication	16 (12.0)
Non-response to medication and ADRs	4 (3.0)
Initiated by the patient	3 (2.3)

(PGx=Pharmacogenetic)

Table 4. PGx testing time frames and documentation procedures

	Total (n=133)
Variable	**n (%)**
PGx test result documented in patient records	70 (52.6)
PGx test result was not analysed, but documented in the patient record	62 (46.6)
PGx test results analysed	25 (18.8)
Time (days) from PGx test referral to result completion mean (SD)	24.8 (18.2)
Time (days) from PGx test referral to completion of result analysis mean (SD)	59.8 (64.6)

(PGx=Pharmacogenetic, SD=Standard Deviation)

DISCUSSION

In this pilot study, the implementation of PGx testing in specialized psychiatric care was examined. More specifically, the study focused on the type of patient groups undergoing testing, the factors leading to testing and how the results were analysed and considered clinically. The study demonstrated that PGx testing particularly targeted patients with a long psychiatric treatment history and multiple previous medication trials. The most common indicated reasons for PGx were medication optimization, and poor response or adverse effects. In addition, testing was most commonly performed in patients diagnosed with psychosis or depression, indicating an emphasis on patients with variable or poor treatment response and variable medication response. The time from laboratory referral to availability of results was nearly one month, and documentation in the patient record took almost two months. There was considerable variability in these time intervals. Most referrals were made at outpatient clinics and hospital wards located near the hospital.

The results are consistent with previous literature, in which pharmacogenetics has been utilized especially in patients with insufficient treatment response or significant adverse drug effects (12,13,14). Previous studies have shown that PGx testing is often directed toward polypharmacy and treatment-resistant patients for whom optimization of pharmacotherapy is challenging (14). The extensive use of antipsychotics and antidepressants prior to PGx testing observed in this study

supports this interpretation. Previous studies have also suggested that pre-emptive PGx testing may reduce adverse drug reactions, improve treatment response and decrease healthcare costs, particularly among psychiatric patients with complex medication regimens (15,16,17). The present findings further support the view that PGx testing is most often utilized in clinically challenging patient populations where medication optimization is particularly relevant.

When examining the indications for testing, the most common indication for PGx test written in the patient health records was optimization of pharmacotherapy, that probably includes insufficient response to medication and/or adverse effects of medication. Surprisingly, polypharmacy was not reported as an indication for PGx in any of the subjects in our sample. However, polypharmacy may still have influenced the decision to refer patients for PGx testing, although this was not explicitly documented in the medical records. It was noteworthy that a significant proportion of tests were performed without a clearly documented indication. This may reflect variability in documentation practices or the possibility that indications for testing are not systematically recorded in patient information systems. This finding highlights the need for more standardized documentation practices in clinical work. Furthermore, the finding raises the question of whether differences in documentation practices and treatment pathways within psychiatry may also be reflected more broadly across the healthcare system, and potentially complicate the interpretation and utilization of patient information in somatic specialized healthcare as well. To our knowledge, the implementation of PGx testing in psychiatric healthcare has been studied only to a limited extent, and previous research has focused primarily on barriers, facilitators and clinical utility rather than on the documentation practices surrounding testing indications and their systematic recording (18).

The clinical utilization of the PGx test results varied. Only approximately half of the PGx test results were clearly documented in patient records, and less than one fifth included a more detailed analysis. This suggests that although the testing itself is being implemented, the systematic use of the results in clinical decision-making has not yet become fully established. Nevertheless, in nearly half of the cases, the results were considered as part of treatment planning, indicating partial integration into clinical practice. Similarly, previous implementation studies have reported that the clinical use of PGx testing results varies considerably: some clinicians actively use the results to support drug selection and dosing, whereas in other cases the results remain undocumented or their impact on clinical decision-making is unclear (14). This reflects the stepwise nature of PGx implementation, with technical availability and clinical integration progressing at different paces (19).

The observed turnaround time for PGx testing in this study is consistent with previous implementation literature. Prior studies have reported that the laboratory phase of pharmacogenetic genotyping typically takes from a few days up to approximately one week, indicating that the analytical process itself is relatively efficient (6,15). In the present study, the average time from test request to result analysis availability was approximately two months, whereas results became available from the laboratory in about one month, suggesting efficiency in the laboratory process itself (Table 4). The overall delay therefore appears to be mainly driven by clinical and organizational factors, such as result processing, documentation and clinical evaluation. This is in line with previous literature emphasizing that key delays in pharmacogenetic implementation are often related to healthcare workflow rather than genotyping itself (6,15).

From a clinical perspective, the findings of this study may support the development of more systematic PGx testing pathways in psychiatric care. The results suggest that clearer criteria for patient selection, more standardized documentation practices and more consistent interpretation of PGx test results could improve the integration of pharmacogenetics into routine psychiatric treatment. In addition, earlier utilization of PGx testing among patients with repeated medication failures or adverse effects may potentially reduce prolonged medication trial processes and improve treatment efficiency.

Interestingly, how and to what extent is PGx testing included in the clinical treatment guidelines? *Table 5* summarizes the recommendations related to PGx testing found in the Finnish Current Care (Käypä hoito) guidelines in the field of psychiatry (20-29). Current Care guidelines do not recommend routine pre-emptive PGx testing, but they may advise considering existing test results or performing testing in cases such as treatment-resistance. Though use of PGx testing is not addressed in many of the guidelines, many of the recommended drugs are such that pharmacogenomic factors may be relevant when treatment is ineffective or adverse effects are unusually severe.

A major strength of this pilot study is the use of real-world clinical data, which provides a realistic view of the practical implementation of PGx testing in psychiatric specialized care. To the best of our knowledge, no previous study has examined the implementation of PGx testing specifically in psychiatric specialized healthcare in this manner. In addition, combining the evaluation of practical testing procedures and patient selection within the same study can be considered a further strength, as it provides a more comprehensive overview of PGx testing

in routine psychiatric clinical practice. Limitations include the retrospective study design and potential deficiencies in patient record documentation, which may particularly affect the accuracy of recording the indications for testing and the reporting of results. In addition, information regarding substance use, and substance-related disorders, was not collected, as it was considered that, given the relatively small sample size, inclusion of these variables would likely not have produced statistically meaningful findings.

The findings of this pilot study can be utilized in clinical practice as well as in the systematic development of PGx testing and the standardization of documentation practices. To conclude, PGx testing seems to be targeted toward general medication optimization and difficult-to-treat psychiatric patients. The clinical utilization and documentation of test results are variable. There is a need for clearer clinical processes and standardized documentation practices to facilitate the integration of pharmacogenetics into psychiatric care.

Table 5. References to the use of pharmacogenetic information in Finnish Current Care Guidelines (Käypä hoito guidelines, the Finnish Medical Society Duodecim, https://www.kaypahoito.fi/en/). The information was collected from the Finnish language guidelines

the Current Care Guideline	How pharmacogenetic information or its use in treatment is presented in the Guideline
ADHD (attention deficit hyperactivity disorder) (20)	Genetic variation in CYP2D6 affects the metabolism of atomoxetine and may influence its plasma concentration.
Anxiety disorder (21)	Pharmacogenetic information improves antidepressant treatment outcomes in depression, but evidence in anxiety disorders is limited; because many medications overlap, testing may help identify atypical metabolism and guide individualized treatment in resistant cases or when adverse effects are unusually severe. Further research is needed to determine the costeffectiveness of broad pharmacogenetic testing.
Depression (22)	Pharmacogenetic information improves antidepressant treatment outcomes in depression. CYP2C19 and CYP2D6 genotyping is justified in treatment-resistant depression to identify atypical metabolism and support individualized medication selection and dosing.
Borderline personality disorder (23)	There is no direct reference to pharmacogenetic information.
Bipolar disorder (24)	In cases of unusually severe, atypical or lowdose adverse effects, pharmacogenetic information may also be applied when relevant. When CYP2D6 genotype is known, it should be considered in dosing aripiprazole, risperidone and haloperidol. Drug level monitoring can help clarify absent response or atypical adverse effects, and CYP2D6 testing may be useful for other CYP2D6 metabolized drugs.
Obsessive-Compulsive Disorder (OCD) (25)	There is no direct reference to pharmacogenetic information.
Schizophrenia (26)	Pharmacogenetic testing may support management of poorly responsive psychosis, particularly with CYP2D6 metabolized antipsychotics or when combining treatment with antidepressants; broader testing still requires costeffectiveness evidence. Drug level monitoring or pharmacogenetic data may help assess unusually severe or atypical adverse effects, although links between CYP polymorphisms and such effects remain inconsistent and need further study.
Eating disorders (27)	There is no direct reference to pharmacogenetic information.
Post-Traumatic Stress Disorder, PTSD (28)	Pharmacogenetic testing can help guide individualized treatment, particularly when drug response is atypical due to significant side effects or insufficient efficacy.
Insomnia disorder (29)	The guideline notes for doxepin that doses below 10 mg generally do not require adjustments for CYP2C19/2D6 variation. Use should be avoided in CYP2D6 ultrarapid metabolizers, while intermediate and poor metabolizers have an increased risk of adverse effects.

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Declarations of interest

None

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REETTA WAHLMAN, MAX KARUKIVI

ALEXITHYMIA AND PARENTAL BONDING AMONG FIRST-VISIT ADOLESCENT PATIENTS IN SPECIALIZED MENTAL OR MEDICAL HEALTHCARE

ABSTRACT

Background: *Alexithymia is a personality trait characterized by difficulties in identifying and describing emotions. In adults, it has been associated with several psychiatric conditions and medical illnesses. Although similar associations appear to exist in adolescents, alexithymia has been studied only rarely in adolescent patient populations. Furthermore, experienced parental bonding has not previously been studied in relation to alexithymia in clinical adolescent samples. Therefore, our aim was to investigate the prevalence of alexithymia and its association with parental bonding among adolescents entering specialized mental or medical healthcare.* ***Methods:*** *The study samples comprised first-visit patients attending an adolescent psychiatry clinic (n=176, aged 13-22 years) or a paediatric clinic (n=117, aged 12-15 years). Alexithymia was assessed using the Toronto Alexithymia scale (TAS-20) and perceived parental bonding with the Parental Bonding Instrument (PBI). The psychometric properties of the TAS-20 were assessed using confirmatory factor analysis and the main analyses were carried out using general linear models.* ***Results:*** *High levels of alexithymic features were prevalent in both samples, with rates of 48.3% in the adolescent psychiatry sample and 19.7% in the paediatric sample. Median TAS-20 scores were significantly higher in the former (60.0 vs. 51.0, p<0.001). Low parental care was significantly related to alexithymic features in both samples. High maternal overprotection had a significant association with alexithymic features only in the adolescent psychiatry sample.* ***Conclusions:*** *Alexithymic features are common among adolescents entering specialized healthcare, particularly among those referred to adolescent psychiatry. Perceived parental bonding is significantly related to alexithymia also among patients referred to paediatric care. Further research is needed to clarify the role of alexithymia in somatic complaints and medical illnesses during adolescence.*

KEYWORDS: ADOLESCENT PSYCHIATRY, ALEXITHYMIA, PARENTAL BONDING, PARENTAL ATTITUDES, PAEDIATRIC PATIENT

INTRODUCTION

Alexithymia is a personality construct, which is characterized by difficulty in identifying and describing feelings and an externally oriented or concrete way of thinking (1). The 20-item Toronto Alexithymia scale (TAS-20) is a widely used self-report questionnaire for assessing alexithymia (2,3). It measures three dimensions of alexithymia: Difficulty Identifying Feelings (DIF), Difficulty Describing Feelings (DDF) and Externally Oriented Thinking (EOT) (2). In Western countries, alexithymia has been reported to be quite common, as the prevalence in general population adults is approximately 10% (4). In samples representing general adolescent populations, the prevalence of alexithymia has been reported to be between 7.3% and 23.5% (5–7).

Interestingly, when comparing younger and older age groups of adolescents, it has been noticed that alexithymia appears to be more prevalent among younger adolescents (5,7). For example, Säkkinen et al. (2007) found that the prevalence of alexithymia among secondary school pupils (median age 14.6 years) was 15.9%, but among 12 to 13-year-olds the prevalence was 21.1% (7). Furthermore, the TAS-20 scores have been observed to decline, at least to some extent, from adolescence to young adulthood (8). Thus, from a developmental perspective, these findings suggest that alexithymia does not represent a personality characteristic that develops during adolescence

per se, but rather a manifestation of underdeveloped emotion processing skills.

However, the psychometric properties of the TAS-20 in younger adolescents have been questioned (9,10). These challenges may reflect difficulties in understanding the questionnaire items as well as the ongoing development of affect regulation. The stability of alexithymia has been shown to be influenced by factors such as concurrent depressive symptoms and psychotherapeutic treatment (11). Taken together, current evidence suggests that during adolescence, alexithymia gradually evolves into the personality trait constellation observed in adulthood, and comprises both stable trait-like and more state-dependent features.

In multiple previous studies, alexithymia has been related to mental disorders and medical conditions, such as depression, eating disorders and diabetes mellitus (12−15). Fewer studies have been conducted among adolescents. Still, an increasing number of studies show an association between alexithymic features and psychiatric illnesses, such as anxiety (16) and depression (17), also in adolescents. Some somatic conditions, such as chronic pain (18) and fibromyalgia (19), have been linked to alexithymia in adolescents, as well as medically unexplained symptoms (20). Regarding the prevalence of alexithymia in mental disorders, for example, over 40% of adult patients with depression have been reported to exhibit high alexithymic features (21) and the prevalence appears to be in the same range for anxiety disorders (22). For medical illnesses, the prevalence of alexithymia also appears to be higher in patient samples compared with general population, for example, in adults with psoriasis 24.8% and atopic dermatitis 27.7% (23,24). In previous studies, the prevalence of alexithymia has ranged from 10% to 53% in patients with multiple sclerosis and from 15% to 52% in patients with fibromyalgia (25,26). However, to our knowledge, the prevalence of alexithymia has not been investigated in adolescent patients in specialized health care.

The relationship between alexithymia and medical illness is likely multifactorial. One potential explanation involves shared risk factors and mental disorders may act as moderating factors in these associations (27). Alexithymia has also been linked to chronic stress (28), which may contribute to the onset and progression of medical illnesses. In addition, lifestyle factors commonly associated with alexithymia, including physical inactivity (29) and unhealthy dietary habits (30) may represent further pathways.

As with many other complex psychological traits, alexithymia is thought to emerge through an interplay between biological and environmental influences. The latter, including dysfunctional parenting and adverse childhood events, have consistently been linked to the development of alexithymic features (31,32). Furthermore, socio-environmental factors, such as maternal low educational level or psychopathology and being an unwanted child, have also been related to alexithymia (6,33,34). Parental bonding refers to the quality of the emotional relationship between a child and their parents or primary caregivers. As a broad indicator of parent-child relationship quality, it has attracted interest in developmental research on alexithymia. Studies in adult populations have shown that less favourable parental bonding is associated with greater difficulties in identifying and expressing emotions (35). Moreover, maternal alexithymic features have been associated with weaker post-partum bonding (36).

Most studies assessing the relationship between parental bonding and alexithymia have used the Parental Bonding Instrument (PBI) (37,38), which measures two dimensions of parenting: care and overprotection. The PBI is a self-report questionnaire in which respondents retrospectively evaluate their parents' behaviour during the first 16 years of life. In a study by Thorberg et al. (2011), a lack of maternal care was found to be particularly related to alexithymia as well as the separate TAS-20 dimensions of DIF and DDF (35). Furthermore, paternal overprotection had a significant but small association with alexithymia. Other studies have also linked maternal overprotection to alexithymia in both adults (39) and late adolescents (40). Most studies investigating the association between alexithymia and parental bonding have been conducted in general population samples or among psychiatric patients. Mannarini et al. (2018) reported a significant association between alexithymia and parental bonding in 12 to 18-year-old adolescent psychiatry patients; however, no further analyses regarding the dimensions of alexithymia were conducted (41). One study investigated the relationship between alexithymia and parental bonding in adult patients with fibromyalgia (42). Interestingly, studies of adults with medical illnesses have tended to highlight paternal bonding dimensions more strongly than maternal dimensions (43,44). In contrast, studies of adult psychiatric populations have more consistently identified maternal dimensions, in particular maternal overprotection, as significant correlates of alexithymia (45,46).

The first aim of the present study was to evaluate the prevalence of alexithymic features in adolescents who enter specialized mental healthcare or paediatric care. The second aim was to assess the relationship between parental bonding and alexithymia, as well as potential differences in this between the two patient groups. To our knowledge, no previous studies have examined these questions in adolescents with medical illnesses. Our hypothesis was that parental bonding, especially

experienced lack of maternal care, would be associated with alexithymia in both patient groups. We also hypothesized, that paternal bonding dimensions would be more strongly associated with alexithymic features in the paediatric sample, whereas maternal dimensions, especially maternal overprotection, would show stronger associations in the adolescent psychiatry sample.

MATERIAL AND METHODS

PARTICIPANTS

The study is part of the research project ´Emotions and wellbeing in adolescents´. The study setting and earlier results have been reported elsewhere (47). The participants for the study were recruited from the Satakunta Hospital District, Finland, which provides specialized healthcare for the inhabitants in the province. The adolescent psychiatry outpatient clinics serve 13 to 22-year-olds and the paediatric clinic offers specialized medical care for 12 to 16-year-old adolescents. The present study comprises two samples, one that was recruited from the adolescent psychiatry outpatient clinics, and another recruited from the paediatric clinic. Both samples were recruited from adolescents, who after a referral were visiting the clinic for the first time. The aim was that the samples would represent actual patient material. Thus, we did not have any particular inclusion or exclusion criteria and all first-visit patients were provided an opportunity to attend the study. A written informed consent was received from all participants, and for adolescents under 15 years of age their guardians also gave their written consent. The guardians of the adolescents at the age of 15 to 17 received a notification of the adolescent's participation. The Ethics Committee of the Hospital District of Southwest Finland gave a favourable opinion of the study (ETMK 89/1801/2017).

Adolescent psychiatry sample

The first sample was from the Satakunta Hospital District adolescent psychiatry clinic and the recruitment phase lasted from November 2017 to December 2018. Participation was offered to all 13 to 22-year-old first-visit patients by the professionals meeting them at the visit. During the recruitment phase, there were altogether 749 eligible first-visit patients. We were not able to collect data on adolescents who refused. In all, 190 participants completed the study questionnaire. However, due to missing data, 14 (7.4%) of them were excluded and the sample in the present study comprises 176 participants.

Paediatric sample

The second sample was recruited from the Satakunta Hospital District paediatric clinic and the recruitment phase lasted from January 2018 to January 2019. Participation was offered by a research nurse to all 12 to 15-year-old first-visit patients at the paediatric clinic. Emergency patients were not recruited. During the recruitment phase, altogether 419 eligible patients visited the clinic for the first time. Research nurse was able to approach 188 of them. Of the potential participants, 34 (18.1%) declined directly. In all, 154 adolescents gave an informed written consent. After receiving the study questionnaire, it was filled in immediately at the clinic or later at home and mailed to the research nurse. Altogether, 12 (6.4%) later refused and 25 (13.3%) did not return the questionnaire. Thus, 117 (62.2%) adolescents who returned the completed questionnaire formed the final sample. Compared with those who refused or dropped out, the participants were more often female (p=0.004), but no significant age difference was found.

MEASUREMENTS

Primary clinical diagnoses

Information on the primary clinical diagnoses was recorded for both study groups to characterize the patient samples. The clinical diagnoses were based on the International Classification of Diseases, Tenth Revision (48). In the adolescent psychiatry sample, information on the primary diagnosis was obtained from patient records following completion of the assessment period. In Finnish clinical practice, this assessment period is conducted by a multidisciplinary team and typically consists of 4–6 visits. In addition to diagnostic assessment, a treatment plan is formulated during this period. The primary diagnoses were categorized into broad diagnostic groups, such as, depression (F32-33), anxiety disorders (F40-42), psychotic disorders (F2X) and eating disorders (F50). In the paediatric sample, the primary diagnoses recorded at the first visit were used, as paediatric services do not employ a comparable assessment period practice. The diagnoses were categorized according to their respective ICD-10 chapters, for example, diseases of the respiratory system (J00-J99), and diseases of the musculoskeletal system and connective tissue (M00-M99).

Background information and traumatic experiences

Since both alexithymia and parental bonding are related to sociodemographic factors, the following variables were included in the analyses: living arrangements (with biological parents/with family of one biological parent/alone or other), occupation/

education (comprehensive school/upper secondary school or higher education/employed/conscription or other), smoking or using snuff (never tried/using irregularly or regularly). Furthermore, traumatic experiences have been associated both with alexithymia and adverse parenting styles and thus, the questionnaire included also questions about possible traumatic experiences (personal experience of a serious accident/victim of violence or sexual assault/death of a loved one/witnessing an accident or a crime/other traumatic experience).

Questionnaire data

Toronto Alexithymia Scale (TAS-20) includes 20 items that are rated using a 5-point Likert scale. The psychometric properties for the TAS-20 scale as a whole and for the DIF (Difficulty Identifying Feelings) and the DDF (Difficulty Describing Feelings) subscales have been shown to be good, whereas the validity of the EOT (Externally Oriented Thinking) subscale is only moderate (2,49,50). TAS-20 has also been shown to be a feasible measure in previous studies with Finnish adolescents (7,51). The TAS-20 total and dimension scores were treated as continuous variables in the main analyses, but also a cut-off score of 61 points or more for categorizing a subject as having high alexithymic features was used.

Parental Bonding Instrument (PBI) questionnaire consists of 25 items and each of them is rated on a 4-point Likert scale (37). Of the items, 12 are related to the Care subscale and 13 to the Overprotection subscale. A low Care subscale score indicates perceived parental neglect, whereas a high score perceived parental affection. A high Overprotection subscale score indicates perceived intrusive parenting and exaggerated control and a low score perceived parental acceptance of a child's autonomy. The instrument has shown strong psychometric properties (52,53). In the present study, the participants assessed separately their mothers and fathers, and the Care and Overprotection subscale scores were used as continuous variables.

Overall Anxiety Severity and Impairment Scale (OASIS) is a short 5-question overall measure of anxiety severity (54,55). OASIS evaluates the intensity of anxiety symptoms, behavioural avoidance and impairment related to anxiety. The OASIS questionnaire is considered to have potential as a general measure of anxiety and has demonstrated excellent reliability and convergent and divergent validity (54). OASIS score was used to measure present distress and anxiety in order to control for them in the analyses.

STATISTICAL METHODS

The normality of the distributions of the continuous variables was evaluated both graphically and with the Shapiro-Wilk test. Because the distributions were non-parametric, medians and interquartiles (IQR) are used to characterize the continuous variables. Group differences between two groups were analysed with the Mann-Whitney U test and between three groups with the Kruskall-Wallis test. Categorized variables were compared using the Chi-Square test. Due to the significant differences between the two samples, the analyses were conducted separately for them. The correlation between the PBI and TAS-20 total and subscale scores was assessed with the Spearman's correlation coefficient.

In order to assess to what extent the PBI scores predicted the TAS-20 total and subscale scores, general linear models (GLM) were utilized. The separate PBI scores that were significantly ($p<0.05$) correlated with the TAS-20 total and dimension scores were included in the GLM analyses. Additionally, the sociodemographic variables that were significantly ($p<0.05$) associated with the outcome variables were included as confounding factors. To evaluate the fit of the models, both the normality and variance of the residuals was assessed. Log-transformed values for the PBI and OASIS scores were used.

A confirmatory factor analysis was conducted to confirm the psychometric properties of the TAS-20 scale in the present study. The comparative fit index (CFI) was 0.89, a score ≥0.90 being acceptable. Chi-square/df was 1.91, a score <3 being good. Additionally, standardized root mean square residual (SRMR) was acceptable at 0.072 (<0.09 being acceptable), along with the root mean square error of approximation (RMSEA) at 0.059 (<0.08 being acceptable). Thus, despite the borderline CFI, these were evaluated as satisfactory.

The internal consistency for the measures was analysed using Cronbach's alpha. While the questionable score for EOT (0.550) was an exception, the scores for the TAS-20 scale and its subscales showed good internal consistency: TAS-20 0.815, DIF 0.843 and DDF 0.736. For the other scales, the scores varied from good to excellent: PBI Mother Care 0.925, PBI Mother Overprotection 0.864, PBI Father Care 0.932, PBI Father Overprotection 0.877 and OASIS 0.917. In all analyses in the study, p-values <0.05 were considered statistically significant. The analyses were conducted using the IBM SPSS software, versions 25.0 and 29.0.

RESULTS

DESCRIPTIVES AND COMPARISONS OF THE ADOLESCENT PSYCHIATRY AND PAEDIATRIC GROUPS

In the adolescent psychiatry sample, there were 121 (68.8%) girls and 55 (31.3%) boys. In the paediatric sample, there were 72 (61.5%) girls and 45 (38.5%) boys. The difference in the gender distribution between the samples was not statistically significant. In the adolescent psychiatry sample, the most common primary diagnostic groups were depression (n=81, 46.0%) and anxiety disorders (n=30, 17.0%). In the paediatric sample, the primary diagnostic groups were musculoskeletal diseases and disorders (n=50, 42.7%) and R00-R99 diagnoses, that is, symptoms and abnormal findings, without a definitive diagnosis of an illness (n=24, 20.5%).

In the adolescent psychiatry sample, the prevalence of high alexithymic features was 48.3% (n=85), while in the paediatric sample the prevalence was 19.7% (n=23) (p<0.001). Altogether 50.4% (n=61) of girls and 43.6% (n=24) of boys were categorized as highly alexithymic in the adolescent psychiatry sample, and 22.2 % (n=16) of girls and 15.6 % (n=7) of boys in the paediatric sample. In both samples, the prevalence difference between girls and boys was not statistically significant.

Regarding age, there was a significant difference between the groups, the paediatric sample being younger. *Table 1* presents the median scores for the continuous variables for all participants, as well as for the two separate samples. The adolescent psychiatry sample had a higher TAS-20 total score (Med=60.00, IQR=15.07) compared to the paediatric sample (Med=51.00, IQR=18.00) with a statistically significant difference (p<0.001). Regarding PBI, the Care subscale scores differed significantly between the groups, both maternal and paternal care being lower in the adolescent psychiatry sample. However, for the Overprotection scores no significant group-wise differences were observed.

Table 1. Comparisons of the continuous variables in the adolescent psychiatry sample and the paediatric sample

	All (n=293)		**Adolescent psychiatry sample (n=176)**		**Paediatric sample (n=117)**		
	Median	IQR	Median	IQR	Median	IQR	P[a]
Age	15.00	4.00	18.00	5.00	14.00	2.00	<0.001
TAS-20 Total Score	57.00	17.50	60.00	15.07	51.00	18.00	<0.001
DIF	19.00	10.45	21.00	8.00	15.00	9.50	<0.001
DDF	15.00	7.00	16.00	6.00	12.97	6.00	<0.001
EOT	23.00	6.00	23.00	6.00	23.00	6.00	0.711
PBI Mother Care	31.00	12.00	28.5	12.00	33.00	10.00	0.005
PBI Mother Overprotection	10.00	11.00	11.00	10.25	10.00	13.00	0.984
PBI Father Care	26.00	15.00	24.00	14.00	30.00	14.00	<0.001
PBI Father Overprotection	8.00	10.00	8.00	10.00	8.50	10.00	0.653
OASIS	8.00	8.00	11.00	6.75	4.00	7.75	<0.001

IQR=Interquartile, TAS-20=20-Item Toronto Alexithymia Scale, DIF=Difficulty Identifying Feelings, DDF=Difficulty Describing Feelings, EOT=Externally Oriented Thinking, PBI=Parental Bonding Instrument, OASIS=Overall Anxiety Severity and Impairment Scale
[a]Mann-Whitney U Test

The younger age of the paediatric sample was also reflected on the differences in the sociodemographic variables (*Table 2*). The majority of the adolescents in the paediatric sample lived with at least one biological parent and were still attending comprehensive school. Adolescents in the adolescent psychiatry sample more frequently reported experiences of being a victim of violence or sexual assault, as well as experiencing other traumatic experiences.

Regarding potential confounding factors, in the adolescent psychiatry sample, none of the sociodemographic variables were significantly associated with the TAS-20 total or DDF scores. Gender was significantly associated with DIF scores (p=0.002), and living arrangements with the EOT scores (p=0.02). In the paediatric sample, gender (p=0.002) was significantly associated with both TAS-20 total (p=0.002) and DIF (p<0.001) scores. Additionally, other traumatic experiences were associated with EOT scores (p=0.001). No significant associations were observed for DDF scores.

Table 2. Comparisons of the categorical variables in the adolescent psychiatry sample and the paediatric sample

		All	**Adolescent psychiatry sample**	**Paediatric sample**	
Variable	Categories	n	n (%)	n (%)	P[a]
Living arrangements (n=290)	With biological parents	142	61 (34.9)	81 (70.4)	<0.001
	With the family of one biological parent	86	56 (32.0)	30 (26.1)	
	Alone or other	62	58 (33.1)	4 (3.5)	
Occupation (n=290)	Comprehensive school pupil	159	56 (32.0)	103 (89.6)	<0.001
	Upper secondary school or higher education student	68	56 (32.0)	12 (10.4)	
	Employed	17	17 (9.7)	0 (0)	
	Other (including conscription)	46	46 (26.3)	0 (0)	
Smoking or using snuff (n=291)	Never tried	158	66 (37.9)	92 (78.6)	<0.001
	Using irregularly or regularly	133	108 (62.1)	25 (21.4)	
Personal experience of a serious accident (n=293)	Yes	13	7 (4.0)	6 (5.1)	0.639
	No	280	169 (96.0)	111 (94.9)	
Victim of violence or sexual assault (n=293)	Yes	26	24 (13.6)	2 (1.7)	<0.001
	No	267	152 (86.4)	115 (98.3)	
Death of a loved one (n=293)	Yes	9	6 (3.4)	3 (2.6)	0.681
	No	284	170 (96.6)	114 (97.4)	
Witnessing an accident or a crime (n=293)	Yes	41	28 (15.9)	13 (11.1)	0.246
	No	252	148 (86.1)	104 (88.9)	
Other traumatic experience (n=293)	Yes	27	25 (14.2)	2 (1.7)	<0.001
	No	266	151 (85.8)	115 (98.3)	

[a]Chi-Square Test

CORRELATIONS BETWEEN ALEXITHYMIA AND PARENTAL BONDING

Due to statistically significant differences between the two samples, the statistical analyses were carried out separately for them. The results of correlation analyses examining the associations between TAS-20 total and subscale scores and PBI scores are presented in *Table 3* for the adolescent psychiatry sample and in *Table 4* for the paediatric sample. In both groups, the TAS-20 total score, as well as the DIF and DDF subscale scores were negatively correlated with the maternal and paternal PBI Care subscale scores. In the adolescent psychiatry sample, the associations with the PBI Overprotection subscale scores were more variable, and none of the associations between TAS-20 scores and paternal Overprotection scores were statistically significant. In contrast, in the paediatric sample, the TAS-20 total score and the DIF and DDF subscale scores were all significantly correlated with both maternal and paternal PBI Overprotection subscale scores.

MULTIVARIATE ANALYSES OF ALEXITHYMIA AND PARENTAL BONDING

Since EOT scores were not significantly correlated with PBI Care and Overprotection scores in either group, separate GLM analyses were not conducted for this outcome. The results of the GLM analyses are showed in *Table 5* for the adolescent psychiatry sample and in *Table 6* for the paediatric sample. In the adolescent psychiatry sample, low maternal Care was significantly associated with DDF subscale scores (adjusted R2=0.301), whereas high maternal Overprotection was significantly associated with TAS-20 total (adjusted R2=0.280) and DIF (adjusted R2=0.358) scores. In the paediatric sample, low maternal Care was significantly associated with higher TAS-20 total (adjusted R2=0.345), DIF (adjusted R2=0.272) and DDF (adjusted R2=0.318) scores. Additionally, low paternal Care was significantly associated with higher DDF scores. Neither maternal nor paternal Overprotection were associated with any TAS-20 scores in the paediatric sample.

Table 3. Spearman´s correlations for continuous variables in the adolescent psychiatry sample (n=176)

	Age	TAS-20	DIF	DDF	EOT	MC	MO	PC	PO	OASIS
Age	–	-0.120	-0.037	-0.061	-0.176*	0.003	-0.113	-0.134	-0.077	0.100
TAS-20	-0.120	–	0.804***	0.827***	0.453***	-0.258***	0.165*	-0.111	0.085	0.503***
DIF	-0.037	0.804***	–	0.656***	-0.21	-0.291***	0.206**	-0.150	0.110	0.565***
DDF	-0.061	0.827***	0.656***	–	0.136	-0.310***	0.124	-0.144	0.103	0.535***
EOT	-0.176*	0.453***	-0.21	0.136	–	0.012	0.036	0.006	0.015	-0.084
MC	0.003	-0.258***	-0.291***	-0.310***	0.012	–	-0.542***	0.352***	-0.242**	-0.252***
MO	-0.113	0.165*	0.206**	0.124	0.036	-0.542***	–	-0.242**	0.382***	0.011
PC	-0.134	-0.111	-0.150	-0.144	0.006	0.352***	-0.242**	–	-0.526***	-0.135
PO	-0.077	0.085	0.110	0.103	0.015	-0.242**	0.382***	-0.526***	–	0.115
OASIS	0.100	0.503***	0.565***	0.535***	-0.084	-0.252***	0.011	-0.135	0.115	–

TAS-20=20-Item Toronto Alexithymia Scale; DIF=20-Item Toronto Alexithymia Scale, Difficulty Identifying Feelings; DDF=20-Item Toronto Alexithymia Scale, Difficulty Describing Feelings; EOT=20-Item Toronto Alexithymia Scale, Externally Oriented Thinking; MC=Parental Bonding Instrument, Maternal Care score; MO=Parental Bonding Instrument, Maternal Overprotection score; PC=Parental Bonding Instrument, Paternal Care score; PO=Parental Bonding Instrument, Paternal Overprotection score; OASIS=Overall Anxiety Severity and Impairment Scale

*p<0.05
**p<0.01
***p<0.001

Table 4. Spearman´s correlations for continuous variables in the paediatric sample (n=117)

	Age	TAS-20	DIF	DDF	EOT	MC	MO	PC	PO	OASIS
Age	–	-0.05	-0.118	0.032	0.022	-0.009	0.105	-0.217	0.055	-0.17
TAS-20	-0.05	–	0.865***	0.882***	0.418***	-0.570***	0.462***	-0.428***	0.434***	0.533***
DIF	-0.118	0.865***	–	0.775***	0.018	-0.525***	-0.437***	-0.361***	0.380***	0.521***
DDF	0.032	0.882***	0.775***	–	0.150	-0.529***	0.457***	-0.387***	0.408***	0.507***
EOT	0.022	0.418***	0.018	0.150	–	-0.149	0.031	-0.188	0.155	0.079
MC	-0.009	-0.570***	-0.525***	-0.529***	-0.149	–	-0.544***	0.714***	-0.458***	-0.489***
MO	0.105	0.462***	-0.437***	0.457***	0.031	-0.544***	–	-0.531***	0.734***	0.387***
PC	-0.217*	-0.428***	-0.361***	-0.387***	-0.188	0.714***	-0.531***	–	-0.555***	-0.513***
PO	0.055	0.434***	0.380***	0.408***	0.155	-0.458***	0.734***	-0.555***	–	0.398***
OASIS	-0.17	0.533***	0.521***	0.507***	0.079	-0.489***	0.387***	-0.513***	0.398***	–

TAS-20=20-Item Toronto Alexithymia Scale; DIF=20-Item Toronto Alexithymia Scale, Difficulty Identifying Feelings; DDF=20-Item Toronto Alexithymia Scale, Difficulty Describing Feelings; EOT=20-Item Toronto Alexithymia Scale, Externally Oriented Thinking; MC=Parental Bonding Instrument, Maternal Care score; MO=Parental Bonding Instrument, Maternal Overprotection score; PC=Parental Bonding Instrument, Paternal Care score; PO=Parental Bonding Instrument, Paternal Overprotection score; OASIS=Overall Anxiety Severity and Impairment Scale
*p<0.05
**p<0.01
***p<0.001

Table 5. Multivariate analysis of the association of the Parental Bonding Instrument (PBI) Care and Overprotection scores with the 20-Item Toronto Alexithymia Scale (TAS-20) total and subscale scores in the adolescent psychiatry sample

Model 1 (TAS-20)				Model 2 (DIF)				Model 3 (DDF)			
	F	df	P[a]		F	df	P[a]		F	df	P[a]
PBI Mother Care	0.064	1	0.801	PBI Mother Care	0.001	1	0.972	PBI Mother Care	4.143	1	0.043
PBI Mother Overprotection	5.844	1	0.017	PBI Mother Overprotection	8.212	1	0.005				
OASIS	56.219	1	<0.001	OASIS	69.497	1	<0.001	OASIS	57.318	1	<0.001
				Gender	1.531	1	0.218				
Intercept	10.658	1	0.001	Intercept	0.941	1	0.333	Intercept	21.626	1	<0.001
Adjusted R^2	0.280			Adjusted R^2	0.358			Adjusted R^2	0.301		

DIF=Difficulty Identifying Feelings, DDF=Difficulty Describing Feelings, PBI=Parental Bonding Instrument, OASIS=Overall Anxiety Severity and Impairment Scale
[a]General Linear Model

Table 6. Multivariate analysis of the association of the Parental Bonding Instrument (PBI) Care and Overprotection scores with the 20-Item Toronto Alexithymia Scale (TAS-20) total and subscale scores in the paediatric sample

Model 1 (TAS-20)				Model 2 (DIF)				Model 3 (DDF)			
	F	df	P[a]		F	df	P[a]		F	df	P[a]
PBI Mother Care	9.906	1	0.002	PBI Mother Care	5.319	1	0.024	PBI Mother Care	9.278	1	0.003
PBI Mother Overprotection	0.020	1	0.887	PBI Mother Overprotection	0.659	1	0.420	PBI Mother Overprotection	1.829	1	0.181
PBI Father Care	3.498	1	0.066	PBI Father Care	3.317	1	0.073	PBI Father Care	5.428	1	0.023
PBI Father Overprotection	1.700	1	0.197	PBI Father Overprotection	0.619	1	0.434	PBI Father Overprotection	0.992	1	0.323
OASIS	11.617	1	0.001	OASIS	6.565	1	0.013	OASIS	7.601	1	0.007
Gender	0.579	1	0.449	Gender	6.631	1	0.012				
Intercept	11.122	1	0.001	Intercept	1.461	1	0.231	Intercept	2.055	1	0.156
Adjusted R^2	0.345			Adjusted R^2	0.272			Adjusted R^2	0.318		

DIF=Difficulty Identifying Feelings, DDF=Difficulty Describing Feelings, PBI=Parental Bonding Instrument, OASIS=Overall Anxiety Severity and Impairment Scale
[a]General Linear Model

DISCUSSION

First, a main finding in this study was that high alexithymic features were prevalent in adolescents entering either specialized mental healthcare (48.3%) or somatic care (19.7%). Second, low parental care was significantly related to alexithymic features in both patient groups. Additionally, high maternal overprotection had a significant association with alexithymic features in the adolescent psychiatry sample, whereas in the paediatric sample, parental overprotection was not significantly related to alexithymic features. To our knowledge, these associations including the three dimensions of alexithymic features have not been previously studied in these types of adolescent patient samples.

Alexithymia was more than twice as common among adolescent psychiatry patients as among paediatric patients (48.3% vs. 19.7%). In the adolescent psychiatry sample, the distribution of primary diagnoses reflected quite well a typical clinical profile, whereas musculoskeletal diseases and disorders were over-represented in the paediatric sample. Compared with previous studies of general adolescent populations, the prevalence of alexithymia in both samples was relatively high, particularly in the adolescent psychiatry sample. However, comparing the paediatric sample with the prevalence reported by Säkkinen et al. (2007) among Finnish 14-year-old adolescents (15.9%), the difference is relatively small (7). Owing to the lack of comparable studies in this age group, direct comparisons are difficult to make. Nevertheless, compared to adult studies, similar prevalence rates for alexithymia have been reported for adult patients with depression or an anxiety disorder (21,22). Interestingly, no significant gender differences in the prevalence of alexithymia were observed in either sample, which is consistent with findings from previous studies in adolescents (5,7).

Low maternal care was significantly associated with DDF scores in the adolescent psychiatry sample. In the paediatric sample, the maternal Care subscale score was linked to the TAS-20 total score and the DIF and DDF dimension scores. Overall, these findings are consistent with previous studies in adults demonstrating robust association between low maternal care and both the TAS-20 total score and its dimensions (35). Interestingly, in a previous study of Finnish adolescents, the association between parental care and alexithymia became non-significant after controlling for current social support (40). However, social support could not be controlled for in the present study. Comparing the two patient groups, the correlation

coefficients between parental and alexithymia were somewhat larger in the paediatric sample. However, in the multivariate analyses, maternal care explained approximately the same proportion of variance in both groups. Although alexithymic traits are clearly influenced by factors beyond parental care, the models including maternal care explained 27−35% of the variance in TAS-20 scores, indicating a medium to large effect size (56).

In the adolescent psychiatry sample, maternal overprotection was associated with both TAS-20 total scores and DIF scores. These findings are supported by the meta-analysis by Thorberg et al. (2011), which demonstrated associations between maternal overprotection and TAS-20, DIF and DDF scores, although these associations were weaker than those observed for maternal care (35). Furthermore, in a study of adolescents from the general population, the association between maternal overprotection and alexithymia was primarily attributable to the DIF and DDF dimensions (40). However, contrary to our expectations, no significant associations between maternal overprotection and alexithymic features were found in the paediatric sample. This was somewhat surprising, given that parental overprotection has been linked to, for example, functional somatic symptoms in adolescents (57). One possible explanation is the over-representation of musculoskeletal diseases and disorders in the sample. However, this interpretation remains speculative.

Paternal care showed no significant associations with TAS-20 scores in the adolescent psychiatry sample. However, low paternal care was significantly associated with higher DDF subscale scores in the paediatric sample. In a study by Mason et al. (2005), higher paternal Care subscale scores were associated with lower TAS-20, DIF and DDF scores in a sample of undergraduate students (58). Furthermore, a previous meta-analysis reported a weak but significant association between paternal Care scores and the TAS-20 total score, whereas associations with the TAS-20 dimensions were non-significant (35).

Taking into account the higher overall paternal Care scores in the paediatric sample, one of the main differences between the two groups appears to be the level of experienced paternal care. This difference may be related to the younger age of the paediatric sample and the fact that these adolescents more often lived with both biological parents. Due to the lack of comparable studies, this interpretation remains speculative. Nevertheless, the role of fathers in the development of alexithymic features during adolescence warrants further investigation. The important role of both mothers and fathers in adolescents' emotional and psychological development has also been emphasized in previous studies assessing alexithymia and parental bonding (41). It is also possible that paternal bonding has specific associations with alexithymic features. In a previous study of adolescents with mental health disorders, those who perceived their fathers as neglectful reported greater difficulties with emotions, which may adversely affect psychiatric outcomes (59).

Associations between EOT scores and the PBI subscales were generally weak, which is consistent with findings from previous studies (40,58). This may reflect the fact that the EOT subscale has repeatedly demonstrated lower reliability and internal consistency than the other dimensions of the TAS-20 questionnaire (49,50). In the present study, the internal consistency of the EOT dimension was also questionable.

In addition to the novel context, a strength of this study was the opportunity to investigate these phenomena in two distinct patient populations. In particular, the paediatric sample was a completely new context for this type of assessment. The attempt to recruit samples that reflect actual patients entering specialized healthcare is also a strength. However, this approach comes with certain limitations, as some selection bias was unavoidable. OASIS scores were strongly associated with TAS-20 scores, particularly in the adolescent psychiatry sample. Given the previously reported strong association between alexithymia and anxiety (16), this is not surprising. Although anxiety was beyond the scope of the present study, controlling for current anxiety symptoms can be considered an additional strength. Nevertheless, some limitations should be acknowledged. Data on both alexithymia and parental bonding were collected solely through self-report questionnaires. Thus, parental care and overprotection reflect participants' subjective experiences rather than objective assessment. Furthermore, the psychometric properties of the TAS-20 in younger adolescents have been questioned. However, the confirmatory factor analysis conducted as a part of the present study supported its psychometric properties, at least in this sample. Another limitation is the relatively small sample size, particularly in the paediatric group.

To conclude, the findings of the present study suggest that alexithymia is common in adolescents entering specialized healthcare. In adult patients, alexithymia has been associated with poorer treatment outcomes in mental disorders (11,60). Therefore, although routine screening for alexithymia in all adolescent patients may not be warranted, considering alexithymic features when evaluating suitability for psychotherapy or inadequate treatment response may be beneficial. Regarding parental bonding, the present findings are consistent with earlier studies and suggest that the associations between alexithymia and parental bonding in adolescents are largely similar to those observed in adults. Furthermore, the links between alexithymia and both mental and somatic illnesses

should be investigated in adolescent patient samples, not only in non-clinical populations. It is plausible that, as in adults, alexithymic features are also related to illness trajectories and recovery in adolescents.

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Declaration of interest

None

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JESSE KANKAALA, ANU-HELMI HALT, MARTTA KERKELÄ, JUHA VEIJOLA, TUULA HURTIG, TIINA RIEKKI

PSYCHIATRIC DISORDERS IN THE OFFSPRING OF MOTHERS WITH ANTENATAL FATIGUE AND STRESS

ABSTRACT

Maternal stress during pregnancy is commonly associated with adverse obstetric outcomes, but long-term psychiatric outcomes of antenatal fatigue in the offspring remain unknown. The aim of this study is to identify potential associations between maternal antenatal fatigue and stress, and offspring psychiatric diagnoses. This study is based on the Northern Finland Birth Cohort 1986 (n=9432 children). Maternal fatigue was assessed with a one-item self-reported question and antenatal stress by elevated blood pressure, blood glucose and hsCRP levels. Cohort members with psychiatric diagnoses were identified using the Finnish Care Register for Health Care. To study associations between maternal stress and fatigue and offspring psychiatric diagnoses, chi-square tests and Cox proportional hazard regression models were conducted utilizing gestational smoking, alcohol use, marital status, maternal education and parental psychiatric diagnoses as confounders. Female offspring whose mothers had fatigue and/or stress had more borderline personality disorders, while male offspring had more mental disorders related to alcohol use and mood disorders, compared to participants without maternal antenatal fatigue or stress. Results suggest maternal antenatal fatigue and stress may have associations with offspring psychiatric disorders, but clinical implications are uncertain. Considering the prevalence of fatigue and stress among pregnant mothers, preventive and supportive interventions could be favourable for offspring.

KEYWORDS: MATERNAL ANTENATAL STRESS, MATERNAL ANTENATAL FATIGUE, PSYCHIATRIC DISORDERS, NORTHERN FINLAND 1986 BIRTH COHORT

INTRODUCTION

Pregnancy is a demanding state in which the mother undergoes physical, physiological, mental and social changes. These changes can increase the risk for the expecting mother to become depressed, anxious, stressed, and, most commonly, fatigued during pregnancy (1–3). Antenatal fatigue is a state of persistent and unrelievable exhaustion which includes physical and mental fatigue (4). Fatigue during pregnancy decreases the quality of life in the form of tiredness, lack of motivation and decreased ability to restore sleep. Studies suggest that 44.4% to over half of expecting mothers experience fatigue during their pregnancy (1,3). Maternal fatigue is suggested to be linked to foetal growth retardation and maternal sleep disturbances, and fatigue may be related to poorer cognitive performance in toddlers at 24 to 36 months (5,6). However, little of maternal fatigue and its long-term effects on offspring are known.

Maternal antenatal stress includes physical, psychological and emotional stressors (7). It is a state that approximately 25 per cent of pregnant women report to suffer from during their pregnancies (8). It seems to be associated with lengthened and premature birth, as well as decreased birthweight in infants and adverse neurodevelopmental outcomes, all of which can have negative long-lasting effects on the offspring (9–12). The effects of maternal stress on the foetus appear to be based on the persistence, duration and time frame of the experienced stress during pregnancy (2,10,13–15). Women suffering from stress during pregnancy show elevated levels of cortisol and untypical production of placental corticotropin-releasing hormone (16,17). Maternal cortisol during pregnancy is mostly inactivated by placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). Maternal antenatal stress is linked to the 11β-HSD2 inhibition leading to elevated cortisol levels in the foetus. Elevated foetal cortisol levels may have adverse effects

on neurodevelopment (2,18,19). Offspring of women suffering from antenatal stress appear to have altered hypothalamic-pituitary-adrenal (HPA) axis reactivity which may leave them vulnerable to behaviour and mental health problems (10).

In Finland, mental disorders are a growing public health concern even though general quality of life and wellbeing have both increased over the years. In the Organisation for Economic Co-operation and Development's (OECD) 2018 report, Finland was leading the charts in the mental illness category, and its cost was reported as 5.3 per cent of gross domestic product (GDP) (€11 billion yearly) (20). In previous years, mental health problems have been the most common reason (around 50 per cent) for disability pension (21). OECD publication from 2022 reports elevated prevalence of mental health problems and anxiety, especially among youth, and an increase in depression among adults between years 2020 and 2022 (22).

Complete mechanisms of maternal stress and the extent of long-term effects on foetus are unclear, yet studies are increasingly recognizing antenatal maternal stress as a significant factor to potential adverse outcomes in offspring (16,23,24). Understanding these potential links between fatigue, maternal stress and psychiatric disorders in offspring could offer us new ways to combat them. The purpose of this study was to examine whether maternal antenatal fatigue and stress either together or separately are associated with offspring lifetime severe psychiatric disorders in a large population-based sample.

METHODS

STUDY COHORT, STUDY DESIGN AND DATA SOURCES

This study examined associations between antenatal maternal fatigue and/or stress and offspring mental disorders in The Northern Finland Birth Cohort 1986 (NFBC1986). NFBC1986 is a prospective Finnish birth cohort study of University of Oulu, from an unselected population in the two northernmost provinces of Finland, that longitudinally observes and studies the cohort members for their health and wellbeing since the foetal period. The cohort consists of 9432 children who were born alive between July 1985 and June 1986 and 9362 mothers. Follow-ups to the cohort members have been regularly conducted, with the latest of them being done between ages 33 and 35 (25).

The collection of cohort data started in antenatal period using two questionnaires, one at early pregnancy and another at third trimester or early postpartum, and by clinical examinations at the antenatal clinics. The antenatal questionnaires were divided by topics, one for background questions such as socioeconomic status, family structure, previous pregnancies and contraceptive use, and another for the mother's current pregnancy (25,26).

MATERNAL STRESS AND FATIGUE (EXPOSURE)

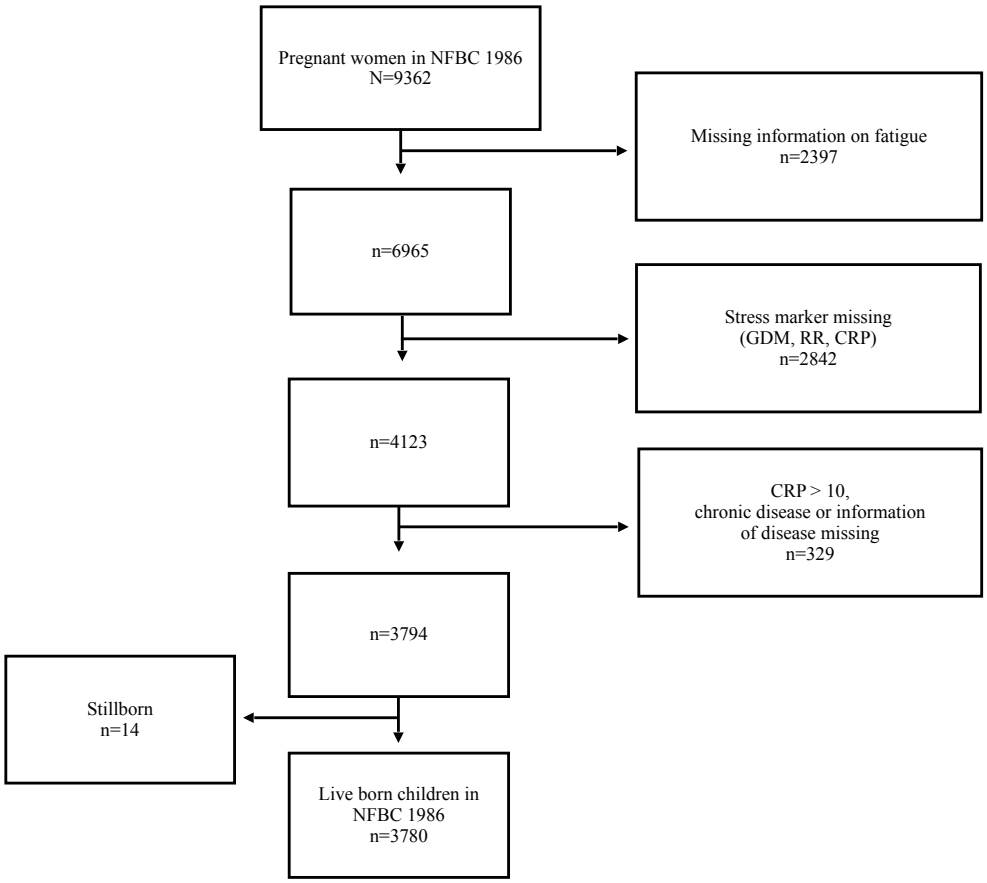
In this study, we used data of mothers (n=3780) from NFBC1986 to measure maternal stress and fatigue during pregnancy as exposure variables (Figure 1). Antenatal fatigue was self-reported with a questionnaire by cohort members' mothers during their last maternity clinic visit or during their postpartum check-up. In the questionnaire the mothers were asked: "How have you felt during this pregnancy?" It was categorized as: 'tired', 'nearly normal' or 'on top of the world'. Mothers who rated themselves as 'tired' were considered as having antenatal fatigue in this study.

Antenatal physical stress was analysed as a sum factor using clinical examination data as well as maternal sera. Maternal antenatal stress was determined by elevated high-sensitivity C-Reactive Protein (hsCRP) levels (3-10), elevated systolic or diastolic blood pressure (sRR>135mmHg or dRR>85mmHg in any measurement) or if the mother had developed gestational diabetes. Clinical examination data was reported on the questionnaire which included blood pressure and blood sugar. Blood pressure was measured on multiple occasions, and if it had been elevated once, it was accounted as a stress marker. Gestational diabetes was determined by elevated glucose levels during oral glucose tolerance test. Maternal sera were taken once from each mother during the first or early second trimester. These samples were available in the Finnish Maternity Cohort of Northern Finland Biobank Borealis. The sera samples included information regarding prenatal hsCRP, thyroid hormones (TSH, T4-V, T3-V) and thyroid antibodies (TPO-Ab).

Final study groups of our study were as following: only fatigue, only stress, both and control group. Mothers who self-reported 'tired' but expressed no antenatal stress markers were labelled 'only fatigue' (n=331), and mothers who did not report 'tired' on the questionnaire but presented elevated levels of any of the stress markers were categorized as 'only stress' (n=1672). Lastly, mothers who reported 'tired' on the questionnaire and expressed stress markers were categorized into a group labelled 'both' (n=446). The control group (n=1331) consists of cohort mothers who didn't qualify as fatigued or stressed. Cohort members' mothers who had missing information on fatigue, had their CRP level above 10 (measured once during pregnancy), had missing information on gestational diabetes or blood pressure were excluded from this study's population

(*Figure 1*). Mothers who had missing information on chronic diseases or suffered from one were also excluded from data analysis to reduce potential confounding.

Figure 1. Participant flow chart of mothers of NFBC1986's cohort members. Flow chart excludes pregnant mothers with chronic diseases or missing information of chronic diseases. Other exclusions happen during or after pregnancy, such as cohort members whose mothers had missing information on stress markers (CRP, blood pressure and blood glucose levels) and withdrawn consent of data use after its collection. Stillborn cohort members, live born twins and triplets have also been excluded



PSYCHIATRIC DISORDERS IN THE OFFSPRING (OUTCOMES)

To examine offspring psychiatric disorders as outcomes, we identified psychiatric diagnoses of cohort members from the Finnish Care Register for Health Care (CRHC). The CRHC (27) provides data on inpatient treatments dating back from 1969 and on specialized outpatient care since 1994 based on International Classification of Diseases (ICD-8-10). The CRHC data was obtained from Findata, the Finnish Social and Health Data Permit Authority, with data permit THL/4442/14.02.00/2023. Findata was responsible for the pseudonymization of the data and ensuring the anonymity of the final results. This data was used to identify offspring mental disorders treated in specialized care from birth up to age 34 (covering the years 1985-2020). The psychiatric disorders were considered severe, as they were treated in specialized care. Because previous research suggests that prenatal exposures may have sex-specific effects (28), we examined psychiatric diagnoses separately by sex.

Psychiatric diagnoses of NFBC1986 members were categorized into main groups. There were seven main diagnostic groups categorized using ICD-10 and corresponding ICD-9 standards. These diagnostic main groups include any psychiatric disorder (F1-F5, F60-F63, F68-F69, F7-F9), disorders diagnosed in childhood or in adolescence (F80-F84, F88-F95, F98), mental

disorders due to psychoactive substance use (F1) (with alcohol and other substances categorized as their own subgroups), mood disorders (F3) (depression-related diagnoses as their own subgroup), neurotic, stress-related and somatoform disorders (F4) (anxiety-related diagnoses as their own subgroup), behavioural syndromes associated with eating, sleep or puerperium (F50, F51, F53), and disorders of adult personality as a main group (F60, F61, F62) and borderline personality disorder as its subgroup. ICD codes used are listed in a *Supplementary Table*. The number of participants with a diagnosis of psychotic and neurodevelopmental disorders was too low (n<5) to be included in the statistical analyses.

CONFOUNDERS

Our confounders for cohort members' parents consisted of self-reported questionnaire data regarding mothers' smoking during pregnancy (yes or no), mothers' alcohol use during pregnancy (yes or no), mothers' marital status (married/cohabiting or other), mothers' education level (basic, secondary or higher) as well as confounders separately for mothers' or fathers' psychiatric diagnosis (yes or no) from CRHC. Parental psychiatric diagnoses included all psychiatric and neurodevelopmental disorder diagnoses recorded in the CRHC between 1972 and 2020. These confounders were chosen due to previous research literature linking antenatal mental health issues to adverse outcomes in offspring (29). They are listed as their own table (*Table 1*).

Table 1. Background characteristics of the study sample

Confounders for both sexes	Control	Only fatigue		Only stress		Both	
	n (%)	n (%)	p-value	n (%)	p-value	n (%)	p-value
n (mothers)	1331	331		1672		446	
Sex of offspring (cohort member)							
Female	634 (47.6)	165 (49.8)	0.509	819 (49.0)	0.485	211 (47.3)	0.949
Male	697 (52.4)	166 (50.2)		853 (51.0)		235 (52.7)	
Mother's smoking during pregnancy							
No	1028 (77.4)	237 (71.8)		1339 (80.1)	0.076	341 (76.5)	0.746
Yes	301 (22.6)	93 (28.2)		333 (19.9)		105 (23.5)	
Mother's alcohol use during pregnancy							
No	1133 (87.5)	276 (85.4)	0.376	1451 (89.0)	0.240	365 (85.5)	0.323
Yes	162 (12.5)	47 (14.6)		180 (11.0)		62 (14.5)	
Mother's marital status							
Married/Cohabiting	1255 (94.3)	320 (96.7)	0.108	1584 (94.7)	0.649	432 (96.9)	0.044*
Other	76 (5.7)	11 (3.3)		88 (5.3)		14 (3.1)	
Mother's education level							
Basic	253 (20.6)	91 (30.1)	<0.001*	389 (25.5)		111 (27.2)	0.016*
Higher	91 (7.4)	12 (4.0)		107 (7.0)		23 (5.6)	
Secondary	882 (71.9)	199 (65.9)		1030 (67.5)		274 (67.2)	

→

Confounders for both sexes	Control	Only fatigue		Only stress		Both	
	n (%)	n (%)	p-value	n (%)	p-value	n (%)	p-value
Parent's psychiatric diagnosis							
Father							
No	1178 (88.5)	300 (90.6)	0.314	1501 (89.8)	0.292	388 (87.0)	0.442
Yes	153 (11.5)	31 (9.4)		171 (10.2)		58 (13.0)	
Mother							
No	1225 (92.0)	291 (87.9)		1539 (92.0)	1.000	394 (88.3)	0.023*
Yes	106 (8.0)	40 (12.1)		133 (8.0)		52 (11.7)	

DATA ANALYSIS

Chi-squared tests were used in cross-tabulations to compare maternal stress and fatigue across background characteristics, which were considered as potential confounders. To analyse the association between maternal stress and fatigue and offspring psychiatric disorders, both descriptive statistics and Cox proportional hazards regression models were applied. The incidence of psychiatric disorders from birth to age 34 was reported and compared between the control group and the three study groups using chi-squared tests. To investigate longitudinal associations, Cox proportional hazards regression models were fitted and stratified by sex to provide separate estimates for men and women. The proportional hazards assumption was formally assessed using scaled Schoenfeld residuals, with no evidence of violation in the global tests.

Both crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) are reported. The adjusted regression models were adjusted for maternal smoking during pregnancy, maternal alcohol use during pregnancy, maternal marital status, maternal education level, maternal diagnosed psychiatric disorder and paternal diagnosed psychiatric disorder. In the regression analyses, emigration or death during follow-up were treated as censoring events. To account for multiple testing across the diagnostic outcomes, p-values from the fully adjusted models were adjusted using the Benjamini-Hochberg procedure to control the false discovery rate (FDR). The correction was performed separately for each exposure category (only fatigue, only stress and both fatigue and stress).

Cumulative incidence functions were generated to provide a visual representation of the development of psychiatric disorders over the follow-up period by sex. The cumulative incidence curves are shown in *Figure 2*. All statistical analyses were performed using R software (version 4.3.1).

In addition, potential selection due to attrition was assessed by comparing participants included in the analytical sample (n=3780) with live-born cohort members not included in the analyses (n=5291) with respect to the study exposures, diagnostic outcomes and potential confounders using cross-tabulations and chi-squared tests.

RESULTS

Our data comprised cohort members of NFBC1986 (n=3780) and their mothers. Of the female offspring, 165 (49.8%) were born to mothers in 'only fatigue' group, 819 (49.0%) to 'only stress' study group and 211 (47.3%) to 'both' study group. Of the male offspring, 166 (50.2%) were in 'only fatigue' study group, 853 (51.0%) in 'only stress' and 235 (52.7%) in 'both' study group.

The descriptive statistics of the study sample are presented in *Table 1*. Mothers who reported only fatigue were less educated compared to other study groups (p<.001) and reported to have smoked more than other study groups during their pregnancies (p=0.041) (*Table 1*). Mothers who suffered from antenatal fatigue and mothers who suffered from both antenatal fatigue and stress were more likely to have received a psychiatric or neurodevelopmental diagnosis compared to other study groups (p=0.024, p=0.023).

Participants included in the analytical sample were generally similar to those not included with respect to the examined characteristics, although mothers of offspring in the non-analytical sample had lower educational attainment and higher levels of fatigue (*Supplementary Table 1*).

MENTAL DISORDERS IN FEMALE OFFSPRING

Female offspring of mothers who had antenatal fatigue presented more borderline personality disorders (BPD) (4.2%) in both crude and adjusted models when compared to female offspring of mothers without antenatal fatigue or stress (1.3%) (HR=4.02, 95% CI 1.40-11.56) (*Table 2*). Female offspring of mothers who suffered from antenatal fatigue and stress also presented BPD more often than control group (3.3%). Adjusted models utilizing potential confounders for female offspring resulted in similar results compared to crude models. A small but statistically significant increase in risk for disorders in adult personality in female offspring of mothers suffering from antenatal fatigue was found in adjusted model (HR=2.29, 95% CI 1.00-5.26). Personality disorders other than BPD were not included due to small study group sizes (n<5). Female offspring whose mothers suffered from antenatal fatigue received more disorders diagnosed in childhood or in adolescence when compared to other study groups. However, the statistically significant finding in crude model lost relevance in adjusted model (HR=1.98, 95% CI 0.96-4.11). After correction for multiple testing, none of the observed associations remained statistically significant at an FDR-adjusted p-value of <.05.

MENTAL DISORDERS IN MALE OFFSPRING

Mental disorders due to alcohol use occurred more often in male offspring whose mothers suffered from both maternal stress and fatigue during their pregnancies compared to control group (7.2% and 4.3% respectively) (HR=1.90, 95% CI 1.03-3.50, adjusted model) (*Table 3*). Mental disorders related to use of other substances were more prevalent in male offspring of mothers who suffered from fatigue (5.4% compared to control 1.7%), with crude model reporting statistically significant finding that lost relevance in adjusted model (HR=2.51, 95% CI 0.96-6.55). Mood disorders in male offspring were most prevalent in 'both' group (10.2%, with control group reporting 6.2%) with both crude and adjusted model having a slight but statistically significant relevance (HR=1.70, 95% CI 1.00-2.88, adjusted model). After correction for multiple testing, none of the observed associations remained statistically significant at an FDR-adjusted p-value of <.05.

Figure 2 represents the cumulative incidence of any psychiatric disorder over the entire follow-up period (ages 0–34 years) by sex. No statistically significant differences between the maternal fatigue and stress groups compared with the control group were observed. The age at onset was earlier in females, but the total cumulative incidences during the whole follow-up were similar between sexes.

Table 2. Associations of cumulative incidences of psychiatric diagnoses and maternal antenatal stress and fatigue in female cohort members

Confounders for both sexes		**Control**	**Only fatigue**		**Only stress**		**Both**	
		n (%)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Any psychiatric or neurodevelopmental disorder	crude adjusted	141 (22.2)	38 (23.0)	1.07 (0.75-1.53) 1.08 (0.75-1.57)	166 (20.3)	0.89 (0.71-1.11) 0.87 (0.69-1.10)	51 (24.2)	1.09 (0.79-1.50) 1.06 (0.75-1.49)
Disorders diagnosed in childhood or in adolescence	crude adjusted	23 (3.6)	12 (7.3)	2.07 (1.03-4.16)* 1.98 (0.96-4.11)	23 (2.8)	0.77 (0.43-1.37) 0.71 (0.39-1.30)	5 (2.4)	0.64 (0.25-1.70) 0.64 (0.24-1.69)
Mental disorders due to psychoactive substance use	crude adjusted	17 (2.7)	7 (4.2)	1.61 (0.67-3.89) 1.60 (0.66-3.87)	30 (3.7)	1.36 (0.75-2.47) 1.23 (0.66-2.28)	5 (2.4)	0.88 (0.32-2.38) 0.85 (0.31-2.32)
Alcohol	crude adjusted	14 (2.2)	6 (3.6)	1.67 (0.64-4.35) 1.70 (0.65-4.45)	20 (2.4)	1.10 (0.56-2.18) 0.96 (0.47-1.97)	5 (2.4)	1.07 (0.38-2.96) 1.06 (0.38-2.95)
Mood disorders	crude adjusted	89 (14.0)	25 (15.2)	1.11 (0.72-1.74) 1.10 (0.70-1.73)	98 (12.0)	0.83 (0.62-1.11) 0.78 (0.58-1.05)	34 (16.1)	1.15 (0.78-1.71) 1.07 (0.71-1.63)
Depression	crude adjusted	81 (12.8)	23 (13.9)	1.12 (0.71-1.79) 1.09 (0.68-1.76)	93 (11.4)	0.87 (0.65-1.17) 0.80 (0.59-1.10)	30 (14.2)	1.11 (0.73-1.69) 1.01 (0.65-1.58)
Neurotic, stress-related and somatoform diseases	crude adjusted	76 (12.0)	20 (12.1)	1.02 (0.63-1.68) 1.01 (0.61-1.68)	92 (11.2)	0.92 (0.68-1.24) 0.89 (0.65-1.23)	26 (12.3)	1.01 (0.65-1.58) 0.98 (0.61-1.57)

Confounders for both sexes		Control	Only fatigue		Only stress		Both	
		n (%)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Anxiety disorders	crude adjusted	43 (6.8)	9 (5.5)	0.81 (0.40-1.66) 0.86 (0.42-1.78)	42 (5.1)	0.74 (0.48-1.13) 0.74 (0.47-1.16)	13 (6.2)	0.89 (0.48-1.66) 0.83 (0.43-1.63)
Behavioural syndromes associated with eating, sleep or puerperium	crude adjusted	19 (3.0)	6 (3.6)	1.22 (0.49-3.06) 1.42 (0.55-3.65)	22 (2.7)	0.89 (0.48-1.64) 0.85 (0.43-1.68)	5 (2.4)	0.78 (0.29-2.09) 0.76 (0.25-2.27)
Disorders of adult personality	crude adjusted	16 (2.5)	9 (5.5)	2.21 (0.98-5.01) 2.29 (1.00-5.26)*	22 (2.7)	1.06 (0.55-2.01) 1.07 (0.55-2.10)	9 (4.3)	1.69 (0.75-3.82) 1.61 (0.68-3.81)
Borderline personality disorder	crude adjusted	8 (1.3)	7 (4.2)*	3.44 (1.25-9.48)* 4.02 (1.40-11.56)*	9 (1.1)	0.86 (0.33-2.24) 1.04 (0.39-2.82)	7 (3.3)	2.62 (0.95-7.24) 3.07 (1.07-8.78)*

Incidences of psychiatric diagnoses of female cohort members of NFBC1986 from the Finnish Care Register for Health Care (CRHC). Psychiatric diagnoses were categorized into main groups using ICD-10 classification. Subgroups are listed below main groups
Adjusted model: adjusted with mother's smoking during pregnancy, mother's use of alcohol during pregnancy, mother's marital status, mother's education level, mother's diagnosed psychiatric disorder and father's diagnosed psychiatric disorder
HR=hazard ratio, CI=confidence interval
*p-value <0.05
After correction for multiple testing, none of the observed associations remained statistically significant at an FDR-adjusted p-value of <.05

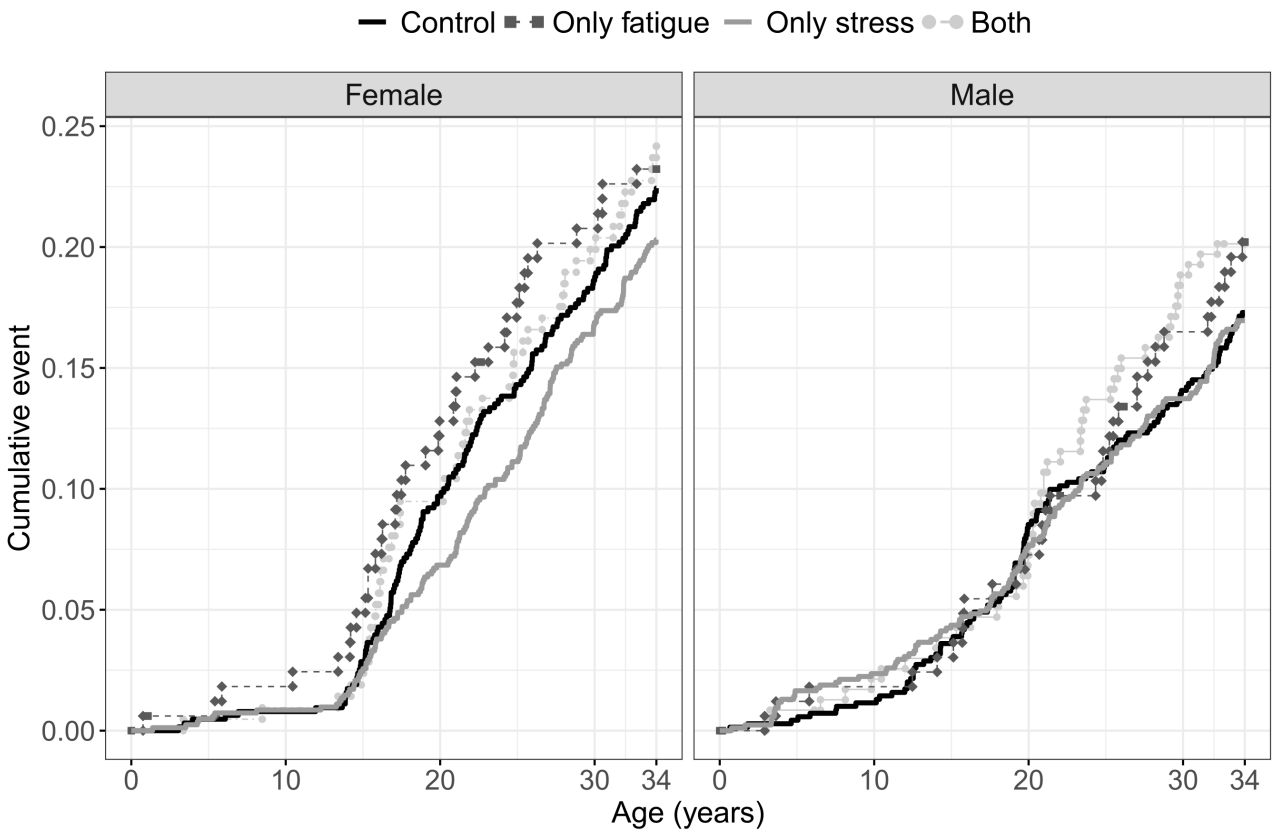
Table 3. Associations of cumulative incidences of psychiatric diagnoses and maternal antenatal stress and fatigue in male cohort members

Confounders for both sexes		Control	Only fatigue		Only stress		Both	
		n (%)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Any psychiatric or neurodevelopmental disorder	crude adjusted	119 (17.1)	33 (19.9)	1.18 (0.80-1.73) 1.13 (0.75-1.70)	143 (16.8)	0.98 (0.77-1.25) 1.00 (0.77-1.30)	47 (20.0)	1.19 (0.85-1.66) 1.27 (0.89-1.81)
Disorders diagnosed in childhood or in adolescence	crude adjusted	26 (3.7)	8 (4.8)	1.28 (0.58-2.84) 1.29 (0.55-3.04)	30 (3.5)	0.94 (0.56-1.59) 0.91 (0.51-1.63)	10 (4.3)	1.14 (0.55-2.36) 1.36 (0.64-2.88)
Mental disorders due to psychoactive substance use	crude adjusted	35 (5.0)	14 (8.4)	1.73 (0.93-3.21) 1.50 (0.77-2.94)	58 (6.8)	1.35 (0.89-2.06) 1.35 (0.87-2.10)	19 (8.1)	1.62 (0.93-2.83) 1.71 (0.95-3.05)
Substance (other)	crude adjusted	12 (1.7)	9 (5.4)*	3.24 (1.37-7.69)* 2.51 (0.96-6.55)	26 (3.0)	1.77 (0.89-3.50) 1.67 (0.81-3.44)	8 (3.4)	1.97 (0.81-4.83) 1.93 (0.75-5.01)
Alcohol	crude adjusted	30 (4.3)	11 (6.6)	1.57 (0.78-3.13) 1.32 (0.62-2.83)	47 (5.5)	1.28 (0.81-2.02) 1.26 (0.77-2.04)	17 (7.2)	1.68 (0.93-3.05) 1.90 (1.03-3.50)*
Mood disorders	crude adjusted	43 (6.2)	12 (7.2)	1.19 (0.63-2.25) 1.04 (0.51-2.09)	52 (6.1)	0.98 (0.65-1.46) 0.99 (0.64-1.53)	24 (10.2)	1.67 (1.02-2.76)* 1.70 (1.00-2.88)*
Depression	crude adjusted	40 (5.7)	10 (6.0)	1.05 (0.53-2.10) 0.86 (0.40-1.86)	51 (6.0)	1.03 (0.68-1.56) 1.03 (0.66-1.59)	18 (7.7)	1.34 (0.77-2.33) 1.46 (0.82-2.58)
Neurotic, stress-related and somatoform diseases	crude adjusted	58 (8.3)	14 (8.4)	1.01 (0.57-1.82) 0.93 (0.49-1.76)	58 (6.8)	0.81 (0.56-1.16) 0.83 (0.56-1.23)	15 (6.4)	0.75 (0.43-1.33) 0.79 (0.44-1.44)

Confounders for both sexes		Control	Only fatigue		Only stress		Both	
		n (%)	n (%)	HR (95% CI)	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Anxiety disorders	crude adjusted	36 (5.2)	10 (6.0)	1.17 (0.58-2.36) 1.10 (0.50-2.44)	36 (4.2)	0.81 (0.51-1.29) 0.94 (0.56-1.56)	9 (3.8)	0.73 (0.35-1.51) 0.81 (0.37-1.79)
Disorders of adult personality	crude adjusted	10 (1.4)	5 (3.0)	2.12 (0.72-6.20) 1.52 (0.47-4.89)	17 (2.0)	1.39 (0.64-3.04) 1.16 (0.51-2.63)	5 (2.1)	1.48 (0.51-4.33) 1.40 (0.48-4.14)

Incidences of psychiatric diagnoses of male cohort members of NFBC1986 from the Finnish Care Register for Health Care (CRHC). Psychiatric diagnoses were categorized into main groups using ICD-10 classification. Subgroups are listed below main groups
Adjusted model: adjusted with mother's smoking during pregnancy, mother's use of alcohol during pregnancy, mother's marital status, mother's education level, mother's diagnosed psychiatric disorder and father's diagnosed psychiatric disorder
HR=hazard ratio, CI=confidence interval
*p-value <0.05
After correction for multiple testing, none of the observed associations remained statistically significant at an FDR-adjusted p-value of <.05

Figure 2. Cumulative incidence of psychiatric diagnoses of cohort members by sex. The graphic shows any psychiatric or neurodevelopmental disorder (F0-F5, F60-F63, F68-F69, F7-F9) variable categorized by study group



DISCUSSION

To the best of our knowledge, this article is the first analysing associations between maternal antenatal fatigue and stress, and offspring psychiatric diagnoses from childhood to adulthood. Our findings suggest that female offspring whose mothers had antenatal fatigue were at increased risk for personality disorders, especially borderline personality disorder compared to control group. The male offspring of mothers with both antenatal fatigue and stress were at increased risk for severe, specialized care-treated mood disorders and mental disorders related to alcohol use. On the other hand, the statistical significance of these findings was low due to low number of participants in the diagnostic groups and multiple testing.

Surprisingly, the offspring of mothers with only stress did not significantly differ from the control group in any of the diagnostic groups. This indicates that in this study setting, where mothers with chronic somatic illness were excluded, common pregnancy complications such as low-grade inflammation, hypertension and gestational diabetes would not be a risk factor for severe mental disorders in the offspring. This is opposite to many previous findings, based on Finnish population (30), and should be further studied.

There were no statistically significant differences between the four study groups regarding the cumulative incidences of mental disorders during the 34-year follow-up, indicating that antenatal fatigue or stress is not associated with different total prevalence or different age at onset for offspring mental disorders. As in earlier literature (30), female participants presented mental health problems at earlier stages of life compared to male participants, most noticeable after the age of 15 years, but the number of psychiatric diagnoses for both sexes remained similar, with male cohort members catching up to female participants after the age of 20 years.

Previous literature explores maternal stress and maternal depression and their correlations regarding offspring outcomes, whereas maternal fatigue and its long-term effects on offspring outcomes have remained less researched. Our study found increase in substance-related disorders in male participants whose mothers had experienced fatigue and stress during their pregnancies. This is in line with previous studies that antenatal stress may influence substance use in offspring, although the exact mechanisms behind these phenomena are not completely understood. Early maternal stress increases dysregulation of the hypothalamic-pituitary-adrenal axis and immune systems which may increase substance abuse and addiction risk, leaving offspring vulnerable later in life (31). Substance abuse later in life may also be indirectly influenced by offspring behaviour, especially externalizing problems (32). Our study also found slight increase in disorders diagnosed in childhood or in adolescence and in borderline personality disorder, particularly in women whose mothers had antenatal fatigue. Exposure to moderate or severe maternal stress appears to be a risk factor for developing a personality disorder later in life for offspring, and that it may act as a non-specific risk factor in mental health disorders generally (33). Fatigue, however, was not measured as an independent variable in these studies.

Previous literature also suggests that antenatal and postnatal depression increase the risk for offspring to suffer from anxiety and depression later in life (34,35). Antenatal depression also may elevate risk for male offspring to develop antisocial personality disorder (36). Previous literature suggests that antenatal stress is linked to offspring mood disorders, schizophrenia and anxiety (33), and our findings suggest that male offspring may be more vulnerable to mood disorders when exposed to maternal antenatal stress and fatigue. Our study, however, had modest results in other categories as there appeared no drastic differences between the study groups of exposure to maternal stress and fatigue. The differences in outcomes may partially be explained by differences in measurement methods, such as our use of questionnaires self-reported by mothers or due to low sample size.

Fatigue may also be described as non-specific symptom, and due to its high prevalence during pregnancy, associations with dramatic outcomes were not expected. In our findings, self-reported maternal fatigue, elevated blood pressure, gestational diabetes and low-grade inflammation did not appear to be strongly associated with serious mental health outcomes in offspring, but fatigue per se and combined with other pregnancy complications may be related to a modest increase in risk of psychiatric disorders.

STRENGTHS AND LIMITATIONS

This study has multiple strengths regarding the data setting and its utilization. Finland has a credible national registry for psychiatric diagnoses that covers the whole population, which makes it a valuable resource for research (37). Northern Finland Birth cohorts provide unique information of northernmost parts of Finland and its population. On the other hand, Finnish population in the 1980s was quite homogeneous and thus the findings of this study may not be generalizable to other populations. Some of the measures utilized during data collection are credible (stress markers such as CRP), and the wellbeing and maternal stress of mothers of the NFBC1986

during their pregnancies have been analysed with both objective and subjective measures. With this data we were able to research sexes separately and detect potential risks for both genders. We were also able to exclude the effects of several maternal chronic and gestational illnesses when evaluating the effects of antenatal fatigue on offspring outcomes.

There are some limitations to this study and its population sample regarding technical issues, collection of data as well as the size of the study sample. The variables regarding maternal psychological wellbeing and stress were limited in the data of NFBC1986 resulting in relatively crude exposure variables. The analytical sample comprised approximately 40% of the original cohort, which may have introduced selection bias and limited the generalizability of the findings. However, attrition analyses indicated that participants included in the analytical sample were generally similar to those not included across most examined characteristics. Differences were observed in maternal education and fatigue, with mothers of non-participants having lower educational attainment and higher levels of fatigue. Although modest statistically significant findings were observed, the low number of participants and statistical bias related to multiple testing decreased the statistical reliability of our findings. Unfortunately, the number of participants in this study was too low to include psychotic disorders in the analyses.

Other limiting factors are information regarding mother's mood and other mental health status during the antenatal period, except for the register-based psychiatric diagnoses. Maternal fatigue was self-reported only once in antenatal period and the question regarding tiredness, despite covering the full gestational period, was vague.

Confounding factors regarding parental psychiatric diagnoses may be incomplete as collection of outpatient records started in 1994 in Finland. Inpatient records go back to 1969, which may also leave information out from this study. Our data does not include outpatient mental health services from primary healthcare for cohort members, as we were only interested in severe mental disorders, assessed by specialized psychiatrist, which increases the validity of the outcome measures.

CLINICAL IMPLICATIONS

Our study has brought some new findings regarding maternal fatigue and stress during pregnancy and their potential effect on increased risk for personality disorders in women and alcohol use disorders and mood disorders in men. Currently, the scientific knowledge on maternal fatigue is limited, and in other study samples there may be other methods to study these associations better. Adequate and timely psychosocial support for pregnant women with fatigue could provide an opportunity to decrease the potential adverse effects of antenatal fatigue. Yet, in this study, common pregnancy complications such as fatigue, low-grade inflammation, gestational diabetes or hypertension were not very significant risk factors for subsequent mental disorders in the offspring, but these findings should be replicated in other studies before any assumptions can be drawn.

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Ethical Considerations

Cohort 1986 33y: Northern Ostrobothnia Hospital District Ethical Committee 108/2017 (15.1.2018)

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Supplementary Material

Supplementary data are available at Psychiatria Fennica online.

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KAISU PAULANTO, PEKKA RAPELI, HENRIK MANNERSTRÖM, NIINA PUUSTINEN, KATINKA TUISKU

THE RELATIONSHIP OF COMPUTERIZED COGNITIVE TEST PERFORMANCE AND RESILIENCE TO WORKING ABILITY AMONG PATIENTS WITH PSYCHIATRIC DISORDERS

ABSTRACT

***Purpose**: We have earlier shown that the ability to work is associated with higher resilience. The aim of this study was to examine whether computerized cognitive test performance distinguishes between clinically defined work ability groups, and how these differences compare to previously established differences in resilience within the same sample. **Methods**: In order to examine these issues in a real-life context, we gathered a sample of 150 consecutive patients between February 2016 and March 2017, who had been referred for a comprehensive psychiatric multidisciplinary assessment of work ability. The subjective, self-rated Resilience Scale and objective, computerized cognitive CANTAB test battery measures of function were compared between three work ability groups: fit for work (28%), partially fit for work (51%) and unfit for work (21%). **Results**: Overall, the unfit group showed the poorest performance on the visual learning task as measured by the Paired Associates Learning (PAL) test, with statistically significant differences observed between the groups. In contrast, the fit for work group displayed significantly higher resilience compared with the partially fit and unfit groups. **Conclusion**: Resilience, rather than objective cognitive test performance, distinguished between patients assessed as fit for work versus those assessed as partially fit or unfit. These findings underscore the importance of addressing resilience within rehabilitation and returntowork interventions. Computerbased neuropsychological test batteries should be interpreted cautiously and used as part of a broader, multidisciplinary assessment when evaluating work ability.*

KEYWORDS: WORK ABILITY, RESILIENCE, CANTAB, COGNITIVE FUNCTION, PSYCHIATRIC DISORDERS

INTRODUCTION

In psychiatric assessments of work ability, the patients' subjective perceptions of their abilities, strengths and symptoms are collected via an interview and often via different structured questionnaires. Self-assessment tools organize the information already gathered and provide information on prognostic self-conceptions and coping resources [1].

The self-evaluation of psychiatric patients is less accurate and varies more than that of the average population. Their responses to subjective questionnaires may reflect fears of returning to work, lack of self-efficacy, lack of insight or expected social secondary gain [2]. Work anxiety may affect their symptom reporting [3]. Depressive patients typically have negative self-expectations [4] and personality disorders often involve difficulties in self-observation [5].

When evaluating psychiatric work ability, data obtained from self-repost measures should be supplemented by other sources of information such as informant reports, observations of behaviour in structured situations and life–outcome data [5]. Standardized cognitive performance tests are also an important source of objective information [6], in addition to anamnestic information on education and work history [7].

In the psychiatric context, the degree and quality of the discrepancy between subjective and objective functional ability is an elementary finding. Although objective findings are essential signs of function, complementary self-assessment tools are helpful in opening the dialogue on the subjective and psychosocial aspects affecting psychiatric rehabilitation and recovery [2]. Psychiatric patients' neuropsychological difficulties are often non-specific and associated with the severity of psychiatric disorders [8] and thus need to be contextualized with other clinical data [7].

Resilience (mental load tolerance, mental flexibility, ability to cope with adversity) has emerged as a psychological concept that is associated with, among other things, depression and recovery from brain injuries [9]. Resilience can be measured using the Resilience scale-14 (RS-14), which has been found suitable for middle-aged patients [10]. Recent scientific literature has found a strong association between resilience and quality of life in people with mental disorders [11].

As a sub-concept of work ability, the term fit for work was originally adopted to change the focus from inability to the remaining ability, considering the specific work of employee [12]. The term work ability is more commonly used in Finland. The idea of residual, or remaining work capacity as well as the fit definitions are quite new [13].

The concept of remaining work ability can also be applied to unemployed persons. The change of paradigm is to assess what the unemployed person can do, or could do with adequate support, rather than focusing on disability. The idea of resource-oriented assessment of work ability is to find out the resources, strengths and remaining work ability [1]. Therefore, in this study we categorized individuals in three groups, fit for work, partially fit and unfit for work according to their work ability apart from their current employment status.

In the previous analysis of this same clinical sample, self-reported resilience (RS-14) was found to be strongly associated with work ability, with significantly higher resilience observed in individuals classified as fit for work compared to those partially fit or unfit [7]. Thus, the association between resilience and work ability in this dataset is already established.

Given that multidisciplinary assessments of work ability already integrate multiple sources of subjective and objective information, it is important to examine the relative contribution of specific assessment methods. Clarifying the role of computerized cognitive testing may help to evaluate its clinical utility as part of a comprehensive assessment process.

Therefore, the aim of this study was to examine whether computerized cognitive test performance (CANTAB) distinguishes between clinically defined work ability groups, and how these differences compare to previously established differences in resilience (RS-14) within the same sample.

METHODS

STUDY FRAME AND ETHICS

We collected data as part of a clinical assessment in the Outpatient Clinic for Assessment of Ability to Work at Helsinki University Hospital (HUS), Finland. The study sample consisted of patients referred to a tertiary-level outpatient unit in specialized psychiatric care specifically for psychiatric work ability assessment. The patients had a prolonged and/or severe disability and their functional status or work ability was contradictory. We obtained ethical approval for the study from the Ethics Committee of Helsinki University Hospital (HUS/81/2017 § 265).

PARTICIPANTS AND PROCEDURE

From February 2016 to March 2017, a total of 248 referrals to the Outpatient Clinic for Assessment of Ability to Work at HUS from occupational health services (37%), public sector specialized care (40%), private practice (9%) or other (14%). The sample (n=150) consisted of Finnish-speaking patients, who completed a profound multidisciplinary clinical assessment and who were able to complete computerized cognitive tests CANTAB (*Figure 1*).

The judgement about being fit, partially fit or unfit for work was based on the following assessment protocol. The psychiatric specialized unit team collected subjective and objective information on the patients. The subjective measures included a lifespan interview conducted by a nurse, various self-report symptom scales and structured SCID I [14] and SCID II [15] diagnostic interviews by psychiatrists, under the supervision of the deputy Chief Psychiatrist. A social worker subsequently collected objective information on the patient's education and employment history. When a more detailed and objective evaluation of functional capacity was indicated, assessments were undertaken by a clinical psychologist, neuropsychologist, occupational therapist or through multidisciplinary collaboration among these professionals, as appropriate. Furthermore, the patient's close ones were interviewed to get information about their daily life and functioning at home. Our clinical protocol included collaboration with occupational healthcare, workplace and employment services (*Table 1*). The assessment period lasted from one to two months and was followed by conclusions of the patient's work ability, as well as a re-evaluation of diagnosis, illness severity, comorbidity and rehabilitation planning with the patient.

Figure 1. Research procedure in the psychiatric specialized unit for assessment of work ability at HUS

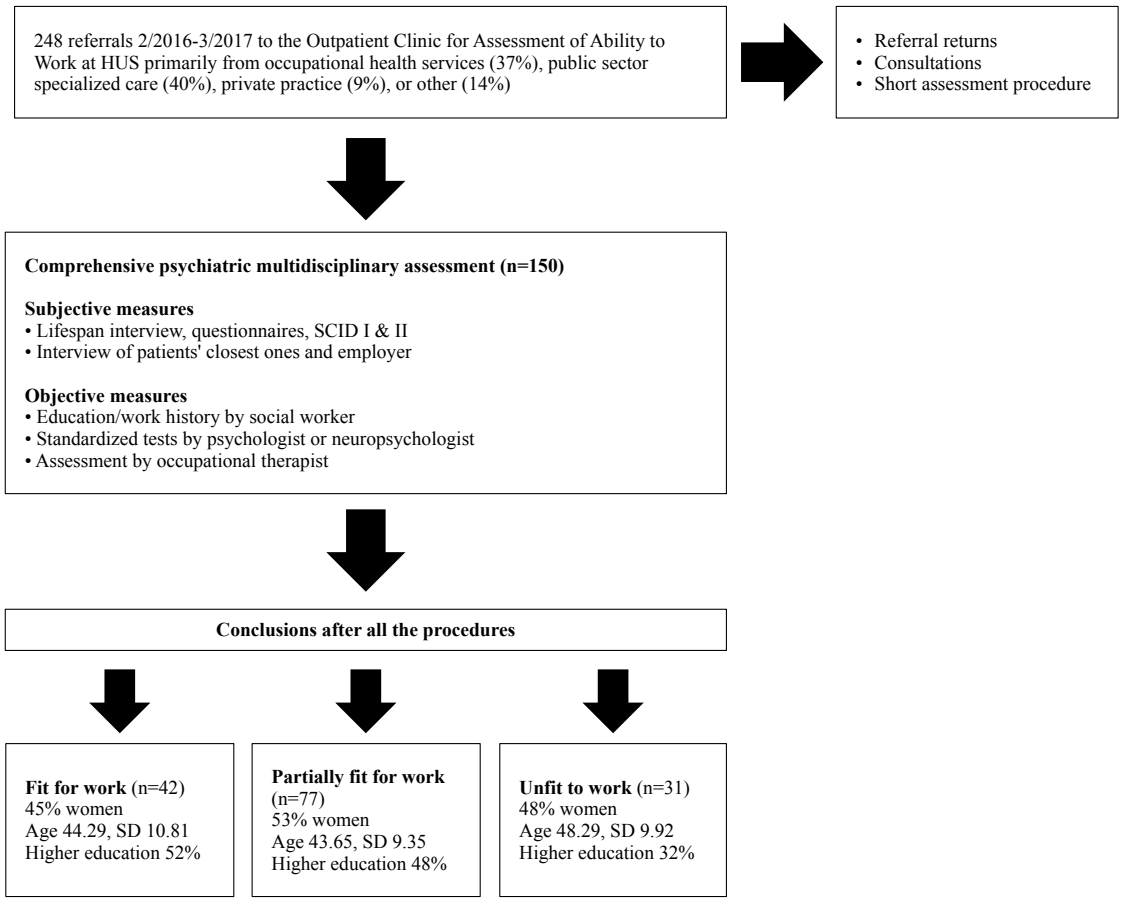


Table 1. Subjective and objective measures of function in psychiatric work ability assessment

	Subjective measures of function	Objective measures of function
Structured situation	Questionnaires Self-assessment tools	The standardized tests of psychologist or neuropsychologist (for example CANTAB)
Half-structured situation	Anamnesis by patient A lifespan interview An interview with the patient´s relative, spouse or employer	Education, work history An assessment of occupational therapist Patient´s behaviour SCID I, SCID-II + Clinical perceptions of psychiatric status

All the patients were diagnosed in accordance with the ICD-10 system [16]. Based on the conclusions following the assessment procedures, the patients were classified into three work ability groups by the consensus of multiprofessional team assessment with network collaboration: fit for work (28%, the "Fit" group, whose psychiatric illness does not affect their ability to work), partially fit for work (51%, the "Partially fit" group, who can be rehabilitated for working life) and unable to work (21%, the "Unfit for work" group, who are permanently unable to work). There were no statistically significant differences in terms of age, sex or education (X^2=5.60; df=4; p=.23) among the three work ability groups in this dataset. *Table 2* presents the psychiatric patients' diagnosis groups and work ability.

MEASURES

Objective ability was assessed using selected CANTAB tests [17,18], which are described below:

Attention Switching Task (AST) measures cued attentional set shifting. The participant is cued to react according to stimulus features or stimulus position, and part of the time the response rule is switching between the two. We considered the % correct responses (bigger is better).

Paired Associates Learning (PAL) is a visual learning task where the participant must learn to associate a visual stimulus with a specific location. The task proceeds relentlessly and becomes incrementally harder as the number of stimuli increases. We considered total errors summed over all trials (smaller is better).

Rapid Visual Information Processing (RVP) requires sustained and divided attention, processing speed and working memory to simultaneously detect three target sequences from background noise in a fast-paced task. We considered measure A, which is a single-variable measure of how well the participant is detecting the target sequences and rejecting non-targets (bigger is better) and total false (smaller is better).

Spatial Working Memory (SWM) requires retention of visuospatial information in a search task and manipulation of remembered items in working memory to avoid repeating past actions. There is no time pressure, but as a self-ordered task it requires formation of a heuristic strategy. We considered the number of between-search errors (smaller is better) and the ability to employ a heuristic strategy (smaller is better).

In addition to cognitive tests the patient's subjective resilience was measured using the Resilience questionnaire, the RS-14. The RS-14 questionnaire includes 14 questions and 5 subcategories: purpose, perseverance, equanimity, self-reliance and existential aloneness (authenticity). The maximum score is 98 points and the lowest 14. Scores in the 14– 56 range are classified as very low, 57–64 as low and 65–73 at the low end. Moderate scores range between 74 and 81 [10]. The psychometric properties of the RS-14 have been found to be good: internal consistency reliability, .87 [9]. Full description of methods is presented in a previous publication [7].

Both the RS-14 and Cambridge Cognition tests CANTAB were supervised by the author, neuropsychologist K.P.

Table 2. Diagnosis groups and work ability of the psychiatric patients

Diagnosis group (primary)	**Fit for work (n=42)**	**Partially fit (n=77)**	**Unfit for work (n=31)**
Mood disorders	9 (21.43%)	57 (74.03%)	17 (54.84%)
Anxiety disorders	13 (30.95%)	10 (12.99%)	4 (12.90%)
Psychosis spectrum	1 (2.38%)	4 (5.19%)	6 (19.35%)
Substance abuse	2 (4.76%)	1 (1.30%)	1 (3.23%)
Personality disorders [a]	9 (21.43%)	1 (1.30%)	2 (6.45%)
Other psychiatric	8 (19.05%)	4 (5.19%)	1 (3.23%)
Total	**42 (100%)**	**77 (100%)**	**31 (100%)**

[a] Primary personality disorder had 12 patients. Comorbid personality disorder had 52 patients

DATA ANALYSIS

The outcomes were analysed with the R statistical program using parametric and non-parametric tests. The continuous outcomes RS-14, RVP A and AST were analysed using the non-parametric Mann–Whitney U-test (Wilcoxon rank-sum test). The U-test was chosen because of small group sizes and non-normal data. The count-based outcomes PAL, RVP total false, SWM between-search errors and SWM strategy were analysed with negative binomial regression. Count-based outcomes are discrete, bounded from below at zero and positively slanted, all of which makes the negative binomial regression a better choice than the U-test.

The non-parametric analysis proceeded in two stages: first, the overall null hypothesis of any differences between the groups was tested with the Kruskal–Wallis test. If the null hypothesis was rejected, all pairwise differences were tested with U-tests and the p-values were Bonferroni corrected. Likewise, the parametric negative binomial regression analysis was performed by first testing the overall null hypothesis with an analysis of variance (ANOVA) as implemented in the MASS package (Venables). If a statistically significant difference was found, Tukey's HSD test was used to analyse all pairwise differences. As 42.7% of the sample had a personality disorder, we also examined their resilience separately.

RESULTS

THE RELATIONSHIP BETWEEN COGNITIVE TEST PERFORMANCE AND WORK ABILITY

For most of the cognitive tests no statistically significant differences between the groups were found. These included Attention Switching task (AST), Rapid Visual Information Processing (RVP) A, Spatial Working Memory (SWM), both between-search errors and strategy.

The Paired Associates Learning (PAL, See *Table 3*) score showed a statistically significant group effect ($p<0.001$). The pairwise comparisons revealed significant differences between Unfit vs. Fit ($p<0.05$) and Unfit vs. Partially fit ($p<0.01$). Patients with better work ability performed better on the PAL test. The difference between Fit and Partially fit was not statistically significant. RVP total false had a statistically significant group effect ($p<0.01$) but none of the pairwise differences reached the statistical threshold.

RESILIENCE AND PERSONALITY DISORDER

As noted before, the fit group had better resilience than the two other groups [7]: Fit for work group (M=72.93), Partially fit (M=56.14), Unfit group (M=52.61). The pairwise tests revealed statistically significant differences between the Fit and the Partially fit ($p<0.001$) as well as the Fit and the Unfit ($p<0.001$).

In our sample 64 (42.7%) of the patients had a primary (12 patients) or comorbid (52 patients) personality disorder: Fit for work group (n=20, 48%), Partially fit (n= 32, 42%) and Unfit group (n=12, 39%). Patients with a primary or comorbid diagnosis of a personality disorder also evaluated their resilience as very low (M=53.03; SD=17.8), which differed highly significantly from those who did not have a personality disorder (M=65.38; SD=17.5) ($p<0.001$).

DISCUSSION

The aim of this study was to examine whether computerized cognitive test performance distinguishes between clinically defined work ability groups, and to compare these findings with previously established differences in resilience within the same sample.

The results showed that the Unfit for work group demonstrated poorer performance compared to the other groups, but only one cognitive variable, visual learning as measured by the Paired Associates Learning (PAL) test, differed significantly between the work ability groups.

Previous findings from this sample, resilience (RS-14) showed the clearest and most consistent differences between the groups. Individuals classified as fit for work reported significantly higher resilience than those classified as partially fit or unfit [7]. As 42.7% of the sample had a personality disorder, we also examined their resilience separately. Patients with a primary or comorbid diagnosis of a personality disorder also evaluated their resilience as very low.

Resilience emerged as the key factor differentiating those fully capable of working from others. The particularly low resilience among depressive patients or patients with a personality disorder, despite sometimes milder objective deficits, may reflect negative self-evaluations [4] or difficulties in self-observation [5].

Across different diagnoses, the severity of symptoms is often more decisive for work ability than the specific psychiatric diagnostic category. While psychotic disorders frequently involve disabling cognitive deficits [19], depression can also include enduring moderate impairment in executive functioning and attention between episodes [20].

Table 3. Demographic characteristics, Resilience (RS-14), Attention shifting task (AST), Paired Associates Learning (PAL), Rapid Visual Information Processing (RVP) and Spatial Working Memory (SWM) of the work ability groups

Variable	Fit for work		Partially fit		Unfit for work	
Group size (n)	42		77		31	
Female %	45		53		48	
University %	52		48		32	
	Mean	SD	Mean	SD	Mean	SD
Age	44	11	44	9.3	48	9.9
RS-14*	72.93	14	56.14	17	52.61	19
AST % correct	94	7.6	93	7.4	89	11
PAL total errors**	20	26	18	22	37	41
RVP A	0.87	0.058	0.88	0.047	0.86	0.056
RVP total false	1.8	3.6	2.4	9	5.1	7.5
SWM errors	28	22	31	20	39	20
SWM strategy	34	6.2	34	6.2	37	6

Note. RVP A n=148, RVP total false n=149, SWM errors and strategy n=149
*significant differences between the Fit and the Partially fit ($p<0.001$) as well as the Fit and the Unfit ($p<0.001$)
**significant differences Unfit vs. Fit ($p<0.05$) and Unfit vs. Partially ($p<0.01$)

STRENGTHS AND LIMITATIONS

A key strength of this study is that data were collected in a naturalistic, realworld setting by a multidisciplinary team. Both resilience and CANTAB data were gathered systematically. Although the database is eight years old, the core clinical issues encountered in psychiatric work ability evaluations remain largely unchanged, supporting the continued clinical relevance of these findings.

Limitations include unequal group sizes and the exclusion of four individuals unable to complete the cognitive tests, meaning the very lowest functioning patients were not represented. The patients of our study had a prolonged or severe disability and/or their functional status or work ability was contradictory, limiting full generalizability to typical occupational health populations with mild psychiatric symptoms. In a naturalistic study design there are always confounding factors, and therefore the results should be interpreted with caution. The analyses used only indicate that differences exist between the groups with respect to the variables examined. The group characteristics show that the group with impaired work ability was the oldest, had the lowest level of education and included the highest proportion of individuals with psychotic disorders.

PRACTICAL IMPLICATIONS

Our findings are clinically meaningful despite methodological challenges. Although CANTAB tests are well validated in experimental research, their utility in naturalistic clinical contexts has been questioned due to psychometric limitations [21,22]. This study supports the view that expectations regarding computerbased neuropsychological tests may be optimistic. PAL might be useful as part of broader neuropsychological assessment. For individuals with severe cognitive impairment (e.g. psychotic disorders or significant learning disabilities) or older age, broader neuropsychological assessment is useful. A neuropsychological assessment is particularly important when a decline in cognitive functioning is suspected in some domains. It can also be used to objectively evaluate the severity of a psychiatric disorder, but contribution should be considered

critically and integrated into a broader, multidisciplinary assessment framework (see *Table 1*).

When disability is primarily driven by cognitive impairment, treatment and rehabilitation should target cognitive deficits and their functional impact. Returntowork planning should include work modifications that accommodate permanent limitations.

When low resilience is the main barrier to work, the focus should shift to enhancing psychological resources through psychotherapy and gradual, supportive work reentry. Even when symptoms or deficits cannot be fully resolved, strengthening resilience may improve returntowork outcomes.

Previous followup studies in similar samples have shown that both objective functional findings and subjective perceptions of capability predict work participation, suggesting that both perspectives reveal relevant rehabilitation targets [23,24].

In psychiatric assessment and rehabilitation, discrepancies between subjective and objective functioning are highly informative and should be discussed openly with patients to foster shared understanding and realistic goal setting. While objective findings are essential, selfassessment tools can facilitate conversations about the psychosocial factors influencing recovery [23,24].

Consistent with recent literature, variations in how resilience is defined and measured contribute to conceptual ambiguity [25]. Nonetheless, in psychiatric assessment it remains important to evaluate how patients perceive and manage adversity.

CONCLUSIONS

Our findings underscore the importance of integrating both subjective and objective assessment in psychiatric disability evaluations. While computerbased cognitive tests provide useful information, their clinical utility may be limited, and results should be interpreted within a broader multidisciplinary framework.

As Stephen Hawking, a model of resilience in the face of profound disability, noted: “However difficult life may seem, there is always something you can do and succeed at. It matters that you just don't give up.”

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Conflict of Interest

The authors declare that they have no conflict of interest.

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LETTER TO THE EDITOR

NICHOLAS ROWE

PREVENTION IS BETTER THAN CURE: ADDRESSING POOR MENTAL HEALTH & WELLBEING IN FINNISH UNIVERSITIES AFTER 50 YEARS OF TREADING WATER

ABSTRACT

Mental health and wellbeing in Finnish Universities has been an issue of concern since the 1960s. Since then, conditions have steadily declined on par with other Western countries, and Finland's general population rates of poor mental health and suicide are among the highest in Europe. National reporting on university student mental health offers an incomplete and somewhat deceptive picture of current conditions, which fails to recognise that university students experience an unexplained 52.6% greater incidence of diagnosable poor mental health than that seen in the general population, and even twice that seen in military veterans in many European countries. Mental health professionals come into contact with only a small proportion of the overall body of university students, and the majority of poor mental health is not seen or diagnosed, including that of those who are driven to take their own lives. Moreover, wellbeing management and counselling is now acknowledged as not being enough to protect university students, yet continues to be the main strategic approach to demonstrating care. Some 1.5 million people in Finland aged 25-64 will have been proportionally affected by the continued historic incidence of poor mental health in Finnish universities, and carry their experiences into their future lives. This likely represents the largest demography for mental health study and intervention, and given the high unexplained incidences for age and sector; government departments, mental health professions, health services and higher education bodies should take urgent steps to investigate the causation of student poor mental health, aiming at prevention over access and cure.

KEYWORDS: UNIVERSITY STUDENT MENTAL HEALTH, FINLAND, STUDENT SUICIDALITY, WELLBEING MANAGEMENT, CAUSATION, PREVENTION, EPIDEMIOLOGY OF MENTAL HEALTH

Reports of poor mental health (PMH) and wellbeing in Finnish universities began in the 1960s. In 1965, 1.2% of the students at the University of Helsinki consulted psychiatrists of the Students' Health Service, and in 1968, '*signs of mental disturbance were found in 23% of the students*' (1), with subsequent incidences consistently ranking with the upper levels of international reports. This early study concluded that '*the facilities for psychiatric treatment available for university students are not adequate at present. It would also be important to develop the mental health counselling services further*', setting the strategic path for addressing PMH in this sector. But mental health conditions have steadily declined on par with other Western countries, and Finland's current rates of poor mental health and suicide are among the highest in Europe (2,3). This is also true for university students and staff, and the EUROSTUDENT VIII report (4) sees Finnish students reporting a steady decline in life satisfaction and a higher prevalence of long-term mental health problems than the EU average. The Finnish Student Health Service (as the sole provider for higher education students in Finland) explicitly defines its primary treatment model around short-term counselling (5). However, a recent admission by US mental health professionals (6) has declared that '*wellbeing management and counselling is not enough to protect university students*'. In the UK, Universities UK and the charity Student Minds have officially declared that student mental health is not just a 'clinical' or 'support' issue, but a 'core strategic' one (7). Furthermore, the National University Mental Health Framework in Australia (8) has stated that the traditional counselling model is reactive and fails to address the structural determinants of mental health.

In 2024, the National Union of Students in Finnish Universities of Applied Sciences SAMOK and the National Union of University Students in Finland (SYL) jointly demanded that the European Union make tackling the mental health crisis among students and young people a priority in its health programme (9). Drawing from basic reported incidences (instigated in conjunction with KELA), in 2000 14–18% of students suffered from mental problems, with 26% experiencing considerable stress, and 12% severe stress (10). In subsequent reports, mental health is measured and reported inconsistently, with different terms and conditions being focused on (11). But incidences of PMH rose to 33% in 2021 and 29% in 2024 which is again consistent with the upper incidences reported in international studies.

WHAT LIES BEHIND THE PERCENTAGES?

National reporting on student mental health offers a somewhat deceptive picture of current conditions, dwelling on 'young person's issues', an awareness of diagnosed conditions and offering shallow observations on care and wellbeing. Behind the small fluctuations of statistics is an unacknowledged situation where university students experience an unexplained 52.6% greater incidence of diagnosable poor mental health compared to the general population (see e.g. 12). In reality, university graduates cover some 39.2% of Finland's population aged 25–34, and 43% of the population aged 25–64 (13), with many more having left university studies for reasons that include mental health issues (estimated at 9.6–25%: see 14,15). Applying comparable international data in the absence of Finnish studies, the following conditions can be seen:

1. Based on comparative student populations for the time (315,600 higher education students), the 2021 reported incidence of 33% of students in universities and colleges in Finland suffering from anxiety and depression (see 16) theoretically entails 104,149 individuals with general PMH symptoms (measured with e.g. Mental Health Inventory scale-type items), and up to 55,440 with Moderate to Severe Anxiety/Depression, representing those who have progressed past 'distress' into territory where clinical intervention or medication would typically be prescribed (measured with GAD-7 (Anxiety) and PHQ-9 (Depression) type tools which look for moderate to severe clinical symptoms).
2. International studies show that the incidences of moderate-to-severe depression and anxiety among *postgraduate students* are likely to be 10-times greater than seen in the general world population (17,18). In Sweden (19), the need for medication for poor mental health increased by 40% from the year before studies to the 5th year of PhD, with no predisposition –– in Finland, this may account for 39,720 students per 4-year cycle, and more with undiagnosed/unreported cases.
3. Incidences of moderate-to-severe depression and anxiety are double those seen in military veterans in many European countries (e.g. 20). In general, untreated episodes of clinical depression can last six to 12 months, with a likelihood of recurrence (21). About two-thirds of people with clinical depression think about suicide and only 25% or fewer may report their condition (22) –– in Finland, this may account for 104,148 unknown students per 4-year cycle
4. 40% of *postgraduate students* experience moderate-to-severe depression and have a 40% increased risk of suicide (23). In the UK: 75% of colleges recorded >5 attempted suicides within the previous 12 months, and 13% over 30 attempts (24). In Sweden over 18 years, suicide accounted for 36.4% of deaths while studying (25). The WHO predict that for every completed suicide, there are 20 attempted suicides (26), and the 2016 KOTT survey (27) found that 5.7% of students had planned for suicide, 3.8% contemplated suicide occasionally, and 1.9% sometimes or often. UK studies (28) have shown 50% of students to have thoughts of self-harm with 42.2% of students having contemplated suicide at least once within the past twelve months (29), and US studies report 7.3% having suicidal thoughts, and 2.3% having plans for suicide (30).

THE COST OF STUDENT POOR MENTAL HEALTH

Loneliness and isolation are key elements of depression across studies, and major global and EU authorities have recently shifted their focus toward loneliness and social isolation as a primary driver of the current student mental health crisis. These reports distinguish between physical isolation (living alone or remote learning) and subjective loneliness (the feeling of being disconnected). The WHO Commission on Social Connection flagship report (2025) explicitly cites that lonely individuals are twice as likely to experience depression compared to those

with strong social ties (31), and the EU Joint Research Centre report on Loneliness Prevalence in the EU (2023-2025) found that young adults (18–25) were more likely to be lonely than the elderly, and highlights a vicious cycle where loneliness triggers depression, and depression further increases social withdrawal (32).

Recent findings on the deteriorating mental health of students in the EU have focused on the combined pressure of academic stress and social isolation (33), and Finnish students have been noted as feeling significantly more isolated from fellow students in their study programme than students in other EU countries (34). Simply saying that '*students feel lonely*' runs a risk of trivialization in the face of more emotionally triggering issues such as violence or terminal disease. But applying WHO data (35) brings home the seriousness of loneliness as a component of PMH: a single average duration episode of major depressive disorder may equate to a mortality risk of smoking 15 cigarettes per day, and smoking one cigarette has been broadly estimated to reduce life expectancy by 11–20 minutes (36). If applied, then relative to duration, general depression with loneliness as a recognised contributory factor may shorten the lives of university students by anywhere from 250 hours (following a 3-month general level incidence) to 1000 hours (24-month duration), and be conservatively estimated to reduce overall life expectancy by 10 to 41 days — in Finland, this may amount to 3,040–12,470 lost years of life.

If the global burden (37) of poor mental health is measured in Disability-Adjusted Life Years (DALYs), it is only surpassed by cardiovascular diseases, respiratory infections, cancers, neonatal disorders and musculoskeletal disorders, and surpasses well-funded and researched health domains such as diabetes, neurological disorders, nutritional deficiencies, HIV/AIDS and STIs, substance abuse, interpersonal violence, conflict and terrorism and natural disasters. The majority of this burden comes from Years Lived with Disability, urging mental health professionals and commentators to reconsider the impact that student experiences (especially those of moderate-to-severe and chronic depression) may have on life beyond university.

STUDENTS ARE NOT JUST YOUNG PEOPLE HAVING A HARD TIME

The oversight and reporting of university student mental health in Finland (and elsewhere) shows a strong degree of paternalism that diminishes the severity of the university student situation. In effect, PMH in this setting is portrayed as something naturally occurring and transient, which is strongly challenged by the evidence of published research. Students are placed as being 'young people' in need of care and guidance, whereas in reality, Finnish students are working-age adults with an average age of 27.3 years on graduation (26.6 EU; 26.7 UK) exceeding international 'young person' classification criteria (UN, WHO, UNICEF and UNESCO have upper thresholds of 24 years old, although OECD extends to 29 years). The vast amount (number of cases) of PMH and suicidality occurs in working-age people aged 19–64, and in the university sector, the most severe PMH is seen in older, competitively selected and more experienced students with a track record of high academic achievement (also visible but unrecognised in the 2024 KOTT report). Against this background, the focus on healthy lifestyle promotion in reports and studies effectually denies the legitimate suffering of those who suffer most.

WHO HAS A DUTY OF CARE, AND WHERE IS PREVENTATIVE MEDICINE?

In the definitions of the World Health Organization (38), anxiety disorders and depression are characterised by '*clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour* [...]' usually associated with distress or impairment in important areas of functioning. Anxiety features '*excessive fear and worry*', and generalised anxiety disorder would account for the majority of experiences recounted in university settings as opposed to panic disorder, social anxiety disorder and separation anxiety disorder implied by 'young person' reporting. Depression is characterized as being '*different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life*', and yet the diagnostic examinations of reports often list incidences of *symptoms* such as feeling sad, loss of pleasure or interest in activities, disrupted sleep, changes in appetite or weight, time spent online, etc., with no attempt to find out the specific triggers that cause more worrying conditions of fear, excessive guilt and low self-worth – feelings that lead to more severe points of hopelessness about the future (which might contribute to reduced performance or withdrawal from studies), or ultimately thoughts about dying or suicide. If unaddressed, these feelings and experiences can influence perspectives of self, worth and ability, and impact many facets of later life (e.g. relationships, employment, health, etc.), as evidenced by the estimations of the impact of poor mental health in terms of Disability-Adjusted Life Years.

Reducing PMH in non-clinical contexts requires the practical reduction/removal of the triggers that cause it. While

attempted suicide is a predictor of suicidality, the actual trigger is likely to be unreported poor mental health in the form of chronic/severe depression and anxiety, with a history indicating a causative and persisting event/condition. This may possibly involve the thoughts of suicide that have been reported in Finnish studies, but even more widely in international literature. But without knowing what these events and conditions are and reducing their occurrence to the lowest possible level, we cannot hope to effectively address mental health and suicide in this population. Of note: most academic papers on student PMH follow wellbeing and percentage incidence reporting patterns (possibly in alignment with funding opportunities), whereas reports into student suicide or endemic PMH in particular, institutions and settings often reveal cases of grave mistreatment and oppressive conditions that have led to the case in question. However, in Finland there has been little to no reporting of university suicides, and PMH in specific institutions is often attributed to 'performance-driven culture' or 'professional training crises' that avoid specific criticism. It is also noticeable that the Finnish media often include an interview with a Finnish Student Health Service (YTHS) psychologist or refer to YTHS statistics to provide a national clinical perspective, reinforcing the idea that this is a public health issue rather than an institutional one.

The belief that an effective management of presented cases through psychotherapeutic counselling and psychiatric intervention will reduce suffering has been shown to be misplaced through worsening situations and statistics outside the clinical domain, and these are seen to be congruent and long-standing in many Western countries. Yet there are few interventions genuinely aimed at prevention in an otherwise healthy student population that extend beyond awareness and voluntary pledges to safeguard mental health. It is also widely acknowledged that mental health professionals come into contact with only a small proportion of university students, and the majority of poor mental health goes unreported or undiagnosed, including among those who are driven to take their own lives. Accordingly, while expert in clinical management and treatment, mental health professionals are not well placed as the sole directors of policy and strategy in this sector, and should seek multi-sectorial assistance from other fields and professions if prevention is considered to be a key obligation of their respective professions.

WORKING TOGETHER

The WHO has been a leading voice in promoting a multi-sectoral approach to PMH, emphasising the need for a whole-of-government and whole-of-society response (39). They advocate for collaboration between health, education, social services, justice and labour sectors to address the social determinants of mental health. Furthermore, the UN Sustainable Development Goals (40) also reflect this approach in SDG 3 which focuses on good health and wellbeing, and includes a target (SDG 3.4) to "*reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and wellbeing*". Roughly estimated, some 1.5 million people in Finland's adult population aged 25-64 have a university-level education, and so will have been proportionally affected by the historic incidence of poor mental health in Finnish universities. This likely represents the largest demography for study and intervention, especially given the high above-population incidences of poor mental health and suicidality for age and sector. Accordingly, even in a country with a comparatively small population, positive reductions in PMH and improvements in overall wellbeing are worth pursuing. The National Mental Health Strategy and Programme for Suicide Prevention 2020-2030 (41) guides decision-making and resource allocation in this field. But although there is an expressed aim to pursue multi-sectorial collaboration, published statements and visible activities still centre on registry reporting and management approaches to PMH, led and guided by mental health professionals, with input from bodies concerned with service provision and cost. Additionally, the emphasis in both elements of the programme is still towards 'young people' and service access/provision.

As an indicator of how invested resources might perform relative to expenditure: the benefit-to-cost forecast in published literature amounts to 2.3/3.0 to 1 when only economic benefits are considered when addressing poor mental health, and 3.3/5.7 to 1 when the value of health returns is also included (42). Given that the WHO cite a global economic cost of US$1 trillion per year from depression and anxiety alone (43), this advisory letter and other reports serve as a continuous call to action for increased investment and revised action in this sector, and highlights the real-world impact of poor mental health in university students.

Offers of further discussion on this important issue would be welcomed.

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