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ORIGINAL ARTICLE

Morbidity and mortality in schizophrenia with comorbid substance use disorders

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Abstract

Objective: Schizophrenia is highly comorbid with substance use disorders (SUD) but large epidemiological cohorts exploring the prevalence and prognostic significance of SUD are lacking. Here, we investigated the prevalence of SUD in patients with schizophrenia in Finland and Sweden, and the effect of these co-occurring disorders on risks of psychiatric hospitalization and mortality.

Methods: 45,476 individuals with schizophrenia from two independent national cohort studies, aged <46 years at cohort entry, were followed during 22 (1996–2017, Finland) and 11 years (2006–2016, Sweden). We first assessed SUD prevalence (excluding smoking). Then, we performed Cox regression on risk of psychiatric hospitalization and all-cause and cause-specific mortality in SUD compared with those without SUD.

Results: The prevalence of SUD ranged from 26% (Finland) to 31% (Sweden). Multiple drug use ($n = 4164$, 48%, Finland; $n = 3268$, 67%, Sweden) and alcohol use disorders ($n = 3846$, 45%, Finland; $n = 1002$, 21%, Sweden) were the most prevalent SUD, followed by cannabis. Any SUD comorbidity, and particularly multiple drug use and alcohol use, were associated with 50% to 100% increase in hospitalization (aHR any SUD: 1.53, 95% CI = 1.46–1.61, Finland; 1.83, 1.72–1.96, Sweden) and mortality (aHR all-cause mortality: 1.65, 95% CI = 1.50–1.81, Finland; 2.17, 1.74–2.70, Sweden) compared to individuals without SUD. Elevated mortality risks were observed especially for suicides and other external causes. All results were similar across countries.

Conclusion: Co-occurring SUD, and particularly alcohol and multiple drug use, are associated with high rates of hospitalization and mortality in schizophrenia. Preventive interventions should prioritize detection and tailored treatments for these comorbidities, which often remain underdiagnosed and untreated.

KEYWORDS

schizophrenia, psychosis, addiction, substance use disorder, mortality

Lähteenvuo and Batalla contributed equally to this work.

1 | INTRODUCTION

Schizophrenia is a serious mental disorder with a lifetime prevalence of about 0.5–1%[1] and accounts for a huge healthcare burden.[2] Schizophrenia is often comorbid with substance use disorders (SUD). Smoking rates are around 65–80%,[3,4] and approximately, 40% of all patients have an additional SUD.[5] There are different hypotheses about the reasons behind the high prevalence of substance misuse in patients with schizophrenia. This comorbidity may stem from gene-environment interactions or shared aetiology, as these disorders share common aetiological factors, both genetic and socioeconomic.[6,7] It is known that substance use increases the risk of developing schizophrenia in genetically vulnerable individuals.[8] With less supporting evidence,[7,9] the 'self-medication hypothesis' assumes that patients use substances in an attempt to treat symptoms of the disease or adverse events from antipsychotics.[10]

Patients with co-occurring schizophrenia and SUD are usually considered difficult to treat by many clinicians as their compliance to outpatient visits and medication adherence may be hampered by their SUD. Therefore, substance use not only appears to increase the risk of developing psychotic symptoms but also negatively affects the course of illness.[11,12] The consequences of substance use can include worsening of psychotic symptoms, treatment nonadherence, interaction with prescribed agents, medical comorbidities, increased violence (both as offenders and victims), and suicides.[12-14] In addition, they show increased service utilization (eg emergency room visits, hospitalizations) and premature mortality.[12-15]

Regarding mortality rates, both schizophrenia and SUD are associated with premature death, with comorbidity showing additive effects.[11,15,16] However, although some substances such as alcohol, heroin and cocaine are considered more lethal compared to other substances such as cannabis, prospective studies have provided conflicting results [ie increased[11,12,16,17] and decreased[18] mortality] or did not take into account that morbidity and mortality might be increased by multiple drug use.[19]

Several studies have examined morbidity and mortality in dual-diagnosis patients with co-occurring schizophrenia and SUD using single cohorts,[11,12,16-18,20-22] but large observational studies exploring the prevalence of SUD sub-groups in patients with schizophrenia, as well as their singular and cumulative associations with prognosis using independent cohorts, are lacking.

1.1 | Aims of the study

This study aims to elucidate both the prevalence of SUD in patients with schizophrenia, as well as the association of these co-occurring disorders with the need for services (ie hospitalization) and mortality, using two large national registries from Finland and Sweden.

Significant outcomes

- In two independent nationwide cohorts of >45,000 individuals with schizophrenia (Finland and Sweden), substance use disorders (SUD) were highly prevalent (at least one in four).
- Any SUD comorbidity in schizophrenia was associated with 50% to 100% increase in hospitalization and mortality risks compared to schizophrenia patients without SUD.
- Elevated mortality risk in schizophrenia patients with SUD was observed especially for suicides and other external causes.

Limitations

- The results are only generalizable to countries with healthcare systems similar to Finland and Sweden.
- Nicotine use disorders were not considered in the analysis because of under-reporting.

2 | METHODS

Data for this study were derived from nationwide registers of Finland and Sweden. The Finnish cohort was identified from the Hospital Discharge register (HDR)[23] as all persons treated due to schizophrenia (the International Classification of Diseases [ICD] codes F20 and F25 [ICD-10]; and 295 [ICD-8 and-9]) in inpatient care during 1972–2014, who were aged <46 years at cohort entry (ie date of first diagnosis).[24] The cut-off age of ≥46 was set in order to avoid oversampling of older patients suffering from somatic health problems (eg respiratory or cardiovascular diseases). Cohort entry was defined as 1 January 1996 for persons diagnosed before that and at the first discharge from inpatient care for persons diagnosed during 1996–2014. Data were collected from the HDR (all hospital care periods with diagnoses, 1972–2017), Prescription register (reimbursed prescription drug purchases, 1995–2017)[25] and causes of death register (1972–2017).[26] The cohort was followed up from cohort entry and until death or 31 December 2017, whichever occurred first. Altogether 30,860 persons were included in the Finnish cohort.

The Swedish cohort was identified from the National Patient Register (NPR, inpatient and specialized outpatient care),[27] disability pensions and sickness absences from the MiDAS register.[28] Persons with schizophrenia were identified

as persons having a recorded diagnosis of schizophrenia (ICD-10 F20, F25) and registered schizophrenia treatment contact between 1 July 2006 and 31 December 2013 in Sweden, at the age <46 years at cohort entry.[29] Cohort entry was defined as 1 July 2006 for persons diagnosed before that and at the first recorded diagnoses for persons diagnosed during July 2006–December 2013. Data were collected from NPR (all hospital care periods and specialized outpatient visits with diagnoses, July 2005–December 2016), the Causes of Death Register (2005–2016)[30] and the LISA register (demographic characteristics).[31] The cohort was followed up from cohort entry and until death or 31 December 2016, whichever occurred first. Altogether 14,616 persons were included in the Swedish cohort.

2.1 | Substance use disorders

Based on diagnoses recorded in inpatient and specialized outpatient care registers, SUD was defined as ICD-10 diagnoses F10-F19 excluding F17 (nicotine dependence). A time-dependent definition was constructed where a person was considered as not having SUD until the first diagnosis and having a 'SUD ever' after the first recording. Definition of SUD was constructed at cohort entry and persons from 'non-SUD' group were transferred to SUD group during the follow-up if they received SUD diagnoses, and their person-time was censored from non-SUD group at this point. Altogether 22,750 persons were included in the non-SUD and 8642 persons in the SUD group in the Finnish cohort; and 10,102 persons in the non-SUD group and 4836 persons in the SUD group in the Swedish cohort during the follow-up.

Four specific SUD were defined, and these were alcohol use only (only alcohol use disorder recorded in the first diagnoses and censored to other substance use), cannabis use, opioid use and stimulant (cocaine, amphetamine/ methamphetamine) use. Cannabis, opioid and stimulant users were allowed to have a comorbid alcohol use disorder, but they were censored to any other SUD subtype. The final category included all other types and multiple drug use (ie two or more SUD and impossible to assess which substance is contributing most to the disorders). Definitions for specific SUD are provided in Table S1. The process of allocating individuals to specific SUD subtypes is illustrated in Figure S1.

2.2 | Outcomes

Outcomes were any psychiatric hospitalization (ICD-10 F00-F99), all-cause mortality and cause-specific mortality, which was categorized as natural causes (A00-R99), suicides (X60-X84, Y10-Y34) and other external causes than suicides (short as 'other external causes', V01–Y98, excluding X60-X84 and Y10-Y34). This last category includes for example poisoning (accidental of undetermined), drowning, inhalation and ingestion of food causing respiratory obstruction or exposure to excessive natural cold. Sensitivity analysis was conducted on hospitalization due to psychosis (F20-F29).

2.3 | Statistical analyses

The analyses were conducted separately in the Finnish and Swedish cohorts. Non-SUD groups served as the reference category in the analyses. Multivariate-adjusted Cox regression models were utilized assessing mortality outcomes and psychiatric hospitalizations comparing persons with SUD to non-SUD. These analyses were adjusted for sex, age at cohort entry, number of previous hospitalizations due to psychosis (≤1, >1–3, >3), time since first schizophrenia diagnosis at cohort entry (≤1, >1–5, >5 years), previous suicide attempt (ICD-10 X60-84, Y10-34), cardiovascular disease (I00-99), diabetes (E10-14), asthma/COPD (J44-46) and previous cancer (C00-97).

The results are presented as adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs).

The Regional Ethics Board of Stockholm approved this research project (decision 2007/762–31). Permissions were granted by pertinent institutional authorities at the Finnish National Institute for Health and Welfare (permission THL/847/5.05.00/2015), the Social Insurance Institution of Finland (65/522/2015) and Statistics Finland (TK53-1042–15).

3 | RESULTS

3.1 | Cohort descriptions and epidemiology

In the Finnish cohort, at cohort entry, 8110 (26%) patients had a SUD diagnosis. The mean age for the Finnish cohort was 32.9 (SD 7.8) years for the SUD group and 33.8 (SD 7.8) years for the non-SUD group. The SUD group had a higher percentage of men (71.9% vs 52.5% for non-SUD, $p < 0.0001$) and more previous hospitalizations than the non-SUD group. Individuals in the SUD group also had a higher prevalence of previous suicide attempts, as well as more somatic comorbidities, despite their younger age. The groups in the Swedish cohort followed a similar pattern, although the prevalence of SUD was higher (4514 [31%] had SUD) and they were slightly older (mean age 34.3 [7.6 SD] for SUD and 35.2 [SD 7.4] for non-SUD) than in the Finnish cohort. These data are shown in Table 1.

The largest SUD sub-group was individuals with multiple drug use (n = 4164, 48% for Finnish; n = 3268, 67% for Swedish cohort), followed by alcohol (n = 3846, 45% for

TABLE 1 Baseline characteristics of schizophrenia patients with and without comorbid substance use disorder (SUD) at the start of follow-up.

	Finnish cohort			Swedish cohort		
	No SUD *N* = 22,750	**SUD *N* = 8110**	***p*-value**	**No SUD *N* = 10102**	**SUD *N* = 4514**	***p*-value**
Mean age (SD)	33.8 (7.8)	32.9 (7.8)		35.2 (7.4)	34.3 (7.6)	
Age categories, % (*n*)			<0.0001			<0.0001
≤25	18.4 (4195)	21.9 (1777)		13.7 (1386)	17.2 (778)	
26–35	34.1 (7752)	36.2 (2938)		31.0 (3134)	33.7 (1521)	
>35	47.5 (10803)	41.9 (3395)		55.3 (5582)	49.1 (2215)	
Male gender, % (n)	52.5 (11936)	71.9 (5830)	<0.0001	58.2 (5880)	70.4 (3177)	0.0030
Number of previous psychiatric hospitalizations, % (*n*)			<0.0001			<0.0001
1	28.0 (6380)	26.1 (2115)		41.3 (4176)	35.1 (1582)	
2–3	32.5 (7394)	30.1 (2440)		22.0 (2222)	20.5 (926)	
>3	39.5 (8976)	43.8 (3555)		36.7 (3704)	44.4 (2006)	
Time since first SCH diagnosis in, years, % (*n*)			<0.0001			<0.0001
≤1	42.9 (9748)	50.7 (4108)		51.5 (5203)	52.6 (2373)	
>1–5	12.2 (2774)	15.3 (1243)		13.5 (1362)	17.1 (771)	
>5	45.0 (10228)	34.0 (2759)		35.0 (3537)	30.4 (1370)	
Previous suicide attempt, % (*n*)	8.4 (1915)	20.8 (1688)	<0.0001	6.1 (620)	21.4 (967)	<0.0001
Cardiovascular disease, % (*n*)	4.8 (1083)	6.8 (548)	<0.0001	3.6 (362)	5.5 (246)	<0.0001
Diabetes, % (*n*)	1.4 (313)	1.8 (146)	0.0067	1.5 (156)	2.7 (121)	<0.0001
Asthma/COPD, % (*n*)	1.9 (424)	3.2 (262)	<0.0001	1.3 (132)	3.1 (140)	<0.0001
Previous cancer, % (*n*)	0.8 (188)	0.9 (73)	0.5335	0.8 (80)	0.9 (40)	0.5598
Median follow-up time in years (IQR)	18.2 (10.0–22.0)	12.1 (6.3–18.2)		9.9 (6.7–10.5)	8.7 (5.6–10.5)	

Finnish; $n = 1002$, 21% for Swedish), cannabis ($n = 420$, 5% for Finnish; $n = 356$, 7% for Swedish), stimulants ($n = 169$, 2% for Finnish; $n = 180$, 4% for Swedish) and opioids ($n = 43$, <1% for Finnish; $n = 57$, 1% for Swedish) (Table S2). All SUD sub-groups had a higher proportion of men than women. At time of entry into the sub-group, cannabis users were the youngest and alcohol users the oldest. Opioid users had the least number of previous SUD hospitalizations, whereas subjects with multiple drug use and alcohol use disorders had the highest number of previous SUD hospitalizations and previous suicide attempts. Results were similar in both cohorts.

3.2 | Hospitalizations

Compared with non-SUD, having any SUD was associated with an increased risk of psychiatric hospitalization (aHR 1.53, 95% CI 1.46–1.61, $p < 0.0001$ for Finnish and 1.83, 1.72–1.96, $p < 0.0001$ for Swedish). Out of the sub-groups, multiple drug use was associated with the highest admission risk (1.50, 1.27–1.65, $p < 0.0001$ for Finnish and 2.25, 1.99–2.55, $p < 0.0001$ for Swedish), followed by alcohol, stimulants and cannabis in the Finnish cohort and alcohol and cannabis in the Swedish cohort (Figure S1). The association with opioid use was not significant in either country. A similar pattern was observed for risk of hospitalization due to psychosis (Figure S2).

3.3 | Mortality

For overall mortality, the crude rate of death per 100 person-years was 12.4% higher for individuals with a comorbid SUD compared to non-SUD in the Finnish cohort (SUD 3.04, 95% CI 3.027–3.045 and non-SUD 2.70, 95% CI 2.697–2.704) and 67% for the Swedish cohort (SUD 2.24, 95% CI 2.227–2.250 and non-SUD 1.34, 95% CI 1.339–1.349). Overall, the patients from the Finnish cohort were at higher risk of death.

The highest increase in risk of mortality for the SUD was for external causes other than suicide (aHR 4.01, 95% CI 3.50–4.61, $p < 0.0001$ for Finnish; aHR 6.05, 95% CI 4.14–8.85, $p < 0.0001$ for Swedish), followed by suicide (1.65, 1.44–1.90, $p < 0.0001$ for Finnish; 2.15, 1.67–2.77, $p < 0.0001$ for Swedish) and natural causes (1.41, 1.24–1.59, $p < 0.0001$ for Finnish; 1.71, 1.22–2.40, $p = 0.0017$

for Swedish) (Figure S2). In general, all-cause mortality was 65% higher for persons with SUD in the Finnish cohort (1.65, 1.50–1.81, $p < 0.0001$) and 117% higher in the Swedish cohort (2.17, 1.74–2.70, $p < 0.0001$) compared with non-SUD. The proportion of deaths by cause of death and incidence rates are shown in Tables S3 and S4, respectively.

Compared with non-SUD, the risk for all-cause mortality was higher for all SUD sub-groups except opioids in the Finnish cohort. In the Swedish cohort, only multiple drug use and alcohol use disorders were associated with a significant increase in all-cause mortality. Alcohol and multiple drug use were associated with a significant increase in mortality due to natural causes in both cohorts, as well as stimulant use disorders in Finland. Alcohol and multiple drug use were associated with a significantly increased mortality due to suicides in both cohorts, as well as cannabis use in Finland. As for mortality due to other external causes, all SUD sub-groups were associated with a significant increase in both countries, except cannabis in Sweden and opioids (no registered events). These results are shown in Figures S3 and S4.

4 | DISCUSSION

This study investigated the prevalence of SUD (excluding nicotine use disorders), use of services (ie hospitalization) and mortality in two large, independent, epidemiologically well-characterized cohorts totalling 45,476 individuals with schizophrenia in two countries. The prevalence of any SUD in patients with schizophrenia was 26% in the Finnish cohort and 31% in the Swedish cohort. The most prevalent SUD were multiple drug use (ie two or more SUD) and alcohol use disorders, followed by cannabis. Any SUD comorbidity, and particularly multiple drug use and alcohol use disorders, were associated with increased risk of psychiatric hospitalization and mortality, especially due to suicides and other external causes, compared to individuals without SUD.

Both cohorts show high prevalence of SUD in patients with schizophrenia, in line with large epidemiological surveys and a recent meta-analysis.[5,32-36] Prevalence of SUD is particularly high in men in both cohorts, which reflects the findings in general population studies.[37] However, an underestimation of the prevalence of SUD cannot be ruled out, as SUD are often underdiagnosed.[38] Underdiagnosis in clinical care may be related to under-reporting,[39] but also to substance-induced symptoms, such as anxiety, depression and psychosis not being recognized as such.[40] Clinicians may also be hesitant to diagnose SUD out of fear that patients will stop coming to their scheduled schizophrenia outpatient visits.[41] All these aspects combined support the notion that there might be a relevant number of undiagnosed SUD in the non-SUD group. This would lead to dilution of the risks associated with SUD, as these undiagnosed individuals would increase the risk in the non-SUD group. It is plausible that SUD are better recognized in Sweden, which would explain the larger prevalence rates and risks associated with SUD in this cohort.

Comorbid SUD have been shown to increase morbidity and mortality rates in schizophrenia.[11,16,21] Here, to our knowledge for the first time, we show the associations of individual SUD with psychiatric hospitalization and mortality in schizophrenia patients in two countries. We omitted nicotine use disorders from our analyses since a large part of them would likely go unrecognized when relying on registers alone. Therefore, we cannot rule out that some of the increased somatic morbidity and mortality observed in the SUD groups stems from nicotine use.[42]

Our results show that psychiatric hospitalization rates were 1.5 to two times higher in patients with schizophrenia and comorbid SUD compared to schizophrenia patients without SUD, in line with previous reports. For example, in a previous Danish 15-year follow-up study with 216 individuals, patients with schizophrenia and comorbid SUD had 2–3 times as many hospitalizations, although their hospitalization stays were on average shorter.[12] In our study, multiple drug use and alcohol use disorders were associated with the highest risks in both countries, followed by stimulant and cannabis use. The results were similar for hospitalizations due to psychosis. It is somewhat puzzling that alcohol use disorder was associated with a higher risk of hospitalization due to psychosis than disorders involving more psychoactive substances such as stimulants or cannabinoids. This could, however, be a reflection of how diagnoses for hospitalizations are used, as patients with schizophrenia admitted for increased anxiety or insomnia may be coded under the schizophrenia diagnosis rather than diagnoses of the lead symptoms. Overall need for psychiatric hospitalizations should thus be considered a more clinically relevant outcome than need for hospitalizations due to psychosis, which is also the reason these results received a higher priority in this study. Unexpectedly, opioid use disorders were not associated with a significantly increased risk of either outcome, which may be due to limited statistical power or due to the hypothesized antipsychotic and anti-anxiolytic effects of opioids.[43] Another possible explanation is the availability of well-established opioid replacement therapy programmes in both countries, participation in which requires regular outpatient visits to addiction services, which may reduce risks for hospitalizations and other negative outcomes, such as mortality.

Overall, mortality was higher in patients with schizophrenia and comorbid SUD compared to those without SUD in both cohorts. The approximately twofold increased mortality observed in both countries is in line with previous reports.[11,16,44] Comorbid SUD was associated with increased mortality by other external causes and suicide,

hinting that unnatural deaths are particularly common in this population group.[11] Alcohol use disorders and multiple drug use were associated with 1.5 to twofold increased all-cause mortality and suicide rates in both cohorts, with even higher risks for other external causes. This highlights the importance of alcohol use disorders and complex combination of SUD on mortality rates in schizophrenia. Cannabis and stimulant use disorders were also associated with increased all-cause mortality but only in the Finnish cohort, which might reflect the limited power and/or shorter follow-up in the Swedish cohort. These results are in accordance with previous reports,[11,12,16,17] except with one study reporting decreased mortality in comorbid psychosis and cannabis users compared to those with a psychotic disorder only.[18] Differences could be related to the limited sample size ($n = 762$) and shorter follow-up period (4–10 years) compared to our study.[18] Finally, our results provide further evidence of the importance of SUD, and particularly alcohol use and multiple drug use, in the assessment of suicide risk in patients with schizophrenia.[45,46] Furthermore, we observed an increased suicide risk in cannabis use disorders only in the Finnish cohort. Cannabis use has been associated in some but not all studies with increased suicide risk, particularly in young adults.[47-49] This may explain the positive association only observed in the Finnish cohort, as Finnish cannabis users were younger compared to Swedish users. However, we cannot rule out that only the Finnish cohort, with a larger sample size, had enough power to detect the increased suicide risk in cannabis users.

The results of this study underscore the importance and prognostic significance of SUD in patients with schizophrenia. However, SUD are often underdiagnosed and go untreated. For example, a cohort study in the UK showed that alcohol use disorders are severely undertreated,[50] as well as opioid use disorders in forensic psychiatric patients with schizophrenia in Finland.[51] This undertreatment of SUD likely holds true for all of them, both for schizophrenia patients as well as the general population. As any SUD was associated with a markedly worse outcome, and the prevalence of multiple drug use was high, it is vital that further steps are taken to better recognize and treat comorbid SUD in patients with schizophrenia.

This study has several strengths and limitations. We investigated comorbid SUD in two nationwide cohorts of persons with schizophrenia, and thus, the results are only generalizable to countries with similar healthcare systems. We cannot entirely rule out that a minority of individuals with schizophrenia remain unidentified (eg misdiagnosed). However, we used registers of contrasted validity,[52] and the characteristics of both health systems (ie universal access, high-quality healthcare standards and subvented health care) facilitate the identification of all patients during the course of illness. Morbidity and mortality outcomes were assessed from nationwide registers in specialized healthcare, covering up-to-date information on all residents and inpatient (both countries) and outpatient (Sweden) treatment and mortality. Our analyses allowed use of alcohol in any of the other specific SUD groups. This is important to note as possibly alcohol contributed to some of the increased risk discovered in the individual SUD groups, especially as previous studies have found that multiple drug users also have more severe alcohol use disorders than alcohol only users.[53] Thus, our results should not be interpreted as increased risk resulting directly from the actual use of a substance, but rather as increased risk in people with the SUD. Still, multiple drug use (ie two or more SUD) was the most common SUD in our study, which likely reflects real-life substance use habits of the study population. In addition, we did not take nicotine use disorders into account in our analysis. Finally, we do not intend to make causality claims, both because this is a register-based observational study, but also due to the fact that many aetiological factors leading to SUD may also inherently increase the risk of the negative outcomes studied here. For instance, childhood abuse has been associated with increased risk for developing psychiatric disorders, including SUD, and thus increased risk for premature mortality and/or service utilization (ie hospitalization).[54] However, recognizing the increased risk associated with SUD should prompt for more diligent efforts in trying to identify these disorders, but also offer effective treatments for them.

SUD are serious comorbidities with substantial negative effects on survival as well as need for services (ie hospitalization) in patients with schizophrenia. Preventive interventions should prioritize detection and tailored treatments for these comorbidities that often remain underdiagnosed and untreated.

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CONFLICT OF INTERESTS

JT, EMR, HT and AT have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. HT reports personal fees from Janssen-Cilag. JT reports personal fees from the Finnish Medicines Agency (Fimea), European Medicines Agency

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DATA AVAILABILITY STATEMENT

The authors are not allowed to make the data used in this study available to the public.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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