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REPRESENTATIVENESS OF CLINICAL ANTIPSYCHOTIC TRIAL SAMPLES WHEN COMPARED WITH A GENERAL POPULATION-BASED SAMPLE

ABSTRACT

Background: Antipsychotics are effective in controlled environments for treatment of schizophrenia. However, there is hardly any research on the effects of antipsychotics in years-long follow-ups in antipsychotic trials. In addition, study samples of the antipsychotic trials differ quite notably from the day-to-day clinical treatment population. In this study, we aimed to compare the population-based Northern Finland Birth Cohort 1966 (NFBC1966) population to the samples in antipsychotic trials using typical inclusion and exclusion criteria found in randomized clinical trials (RCTs). We also compared long-term outcomes of individuals with schizophrenia meeting and not meeting inclusion criteria for clinical trials.

Method: We gathered clinical antipsychotic trials and their inclusion and exclusion criteria. These inclusion and exclusion criteria were compared to the data of NFBC1966 to find out how many of the 54 participants in NFBC1966 34-year follow-up would meet these criteria, and how representative outcomes of the clinical antipsychotic trials are compared to a longitudinal population-based sample.

Result: Depending on how strict the inclusion and exclusion criteria of the RCTs were, 10.5 to 24.6 per cent of the participants in the NFBC1966 34-year follow-up could have been included in RCTs using the criteria. Notably, 42.1 per cent of the participants in the NFBC1966 would be excluded without considering PANSS as inclusion criteria. There was no statistically significant difference in the distribution of PANSS and SOFAS scores between the included and excluded groups in longitudinal analysis. However, in the distribution of hospital treatment days in the groups included and excluded by criteria of RCTs, there was a statistically significant difference between the groups.

Conclusions: Over one-third of the participants of this population sample could have been excluded from clinical trials without even considering psychotic symptoms as an inclusion criterion.

KEYWORDS: SCHIZOPHRENIA, ANTIPSYCHOTIC TRIALS, POPULATION-BASED, REPRESENTATIVENESS, INCLUSION AND EXCLUSION CRITERIA

INTRODUCTION

Schizophrenia is globally seen as one of the most serious and disabling mental illnesses, where the early starting age of the disease and the severe symptoms often lead to severe effects on day-to-day life and performance. The global prevalence of the disease is estimated to be slightly less than one per cent, and in Finland, it is estimated to be around one per cent, which means around 50 000 individuals with schizophrenia in Finland[1]. The baseline for treatment of schizophrenia is early recognition of the disease, a long-sustained care relationship and personalized care planning, which often includes of the use of antipsychotic medications [2,3].

Antipsychotics, especially long-acting injections, are proven to be effective in controlled environments for positive symptoms and prevent recurrence after remission [4,5]. However, there is hardly any research about antipsychotics' effect on negative symptoms and adverse effects in years-long follow-ups. According to Leucht et al., in 65 randomized controlled trials (RCTs), the median duration of follow-up was 26 weeks and there were only a few 3-year follow-ups [6].

The essential difference between samples in antipsychotic RCTs and patient material in the clinical real world is the relatively narrow inclusion and exclusion criteria in RCTs. Clinical drug trials' inclusion and exclusion criteria are meant to confirm that patient material is homogeneous, and that the tested drug is used on an individual who has the disease meant for the medicine in question. Inclusion and exclusion criteria are used to select patients whose disease is severe enough, but not so severe that there would not be any expected positive outcome. Therefore, the selection of patient material in clinical trials may differ greatly from clinical patient material. The psychiatric conditions of patients in clinical trials of mental illnesses are milder than in ordinary clinical patient material. In addition, comorbidities are more often met with clinical real-world patients, and in some cases patients' daily function is much worse compared with individuals in clinical drug trials. When comparing randomized controlled trials to the clinical world, the difference between efficacy and effectiveness has to be noted [7].

The differences between RCTs and the clinical real-world patient samples are also acknowledged in the terminology of the effect of medications, for example, antipsychotics. Efficacy is defined as an expected end result under ideal circumstances, for example, in RCT designs, and the effectiveness indicates effects in a more realistic setup with more interfering factors in the real-world population [8].

In this study, the aim was to compare the characteristics of persons with schizophrenia in a general population sample to inclusion and exclusion criteria of clinical antipsychotic trials. The general population sample was drawn from the Northern Finland Birth Cohort 1966 (NFBC1966). As Kennedy-Martin et al. [7] predicts and as a hypothesis for this study, we assume that individuals with schizophrenia in the NFBC1966 are more severely ill and have more comorbidities than the clinical antipsychotic trial material. Accordingly, it is also assumed that only a small part of the NFBC1966 population with schizophrenia could be included in an average clinical antipsychotic trial. We also aimed to compare the outcome of this presumably small population of individuals meeting the inclusion and exclusion criteria to the population not meeting the criteria.

NFBC1966 has been active on schizophrenia for over 30 years. During that time, the longitudinal research has allowed various risk factors to be found, for example, parental psychosis and delays in normal growth in the early stages of childhood [9]. Because of the wide variety of outcomes and general heterogeneity of schizophrenia as a disease, there has been meaningful study on predictors for different outcomes of the disease, even the use of antipsychotics as a predictor. For example, according to Moilanen et al. [10], cumulative high dosage and long-term use of antipsychotics, especially polypharmacy, was associated with unfavourable outcomes, and steady low dosage use was more favourable.

MATERIAL AND METHODS

THE NORTHERN FINLAND BIRTH COHORT 1966

The Northern Finland Birth Cohort 1966 (NFBC1966) is a longitudinal population-based sample, with collection having begun during the antenatal period of the participants. It includes 96 per cent of individuals (12 058 liveborn) that were expected to be born in 1966 in the area of Northern Finland [11,12]. NFBC1966 differs from randomized controlled trials (RCT), especially in the way persons with schizophrenia are involved in the sample. People affected by schizophrenia are not involved via healthcare or drug trial, they are involved as an individual in a part of cohort research and involved as a part of schizophrenia research via several nationwide registers.

During the years 1999 to 2001, a 34-year follow-up was performed in the NFBC1966. Individuals who had had a psychotic episode by the year 1997 were invited

to participate. Altogether 91 individuals with psychosis, of which 61 had a schizophrenia diagnosis, participated. Participants were imaged with MRI and interviewed with questions of, for example, use of antipsychotics, symptoms, somatic diseases and substance abuse. Based on the interview, different assessments, for example, Positive and Negative Syndrome Scale (PANSS), Clinical Global Index (CGI) and Social Occupational Functioning Assessment Scale (SOFAS) were conducted. During the years 2008 to 2010, a new follow-up at the age of 43 years was carried out. The 43-year follow-up also included 107 individuals who had had a psychotic disorder between the years 1998 and 2008, of which 54 were with schizophrenia. The research protocol was the same as outlined. Altogether 40 individuals with schizophrenia attended both the 34-year follow-up and the 43-year follow-up. Four of these individuals left the cohort study making the total participants of both studies 36[10].

GATHERING AND EVALUATION OF THE INCLUSION AND EXCLUSION CRITERIA IN THE CLINICAL TRIALS

To map out the representativeness of individuals in antipsychotic trials, recent meta-analyses of antipsychotic trials of schizophrenia were evaluated. Based on representativeness and the minor number of first-episode studies, we chose two meta-analyses by Leucht et al. [13,14]. Leucht et al. (2013) included 212 trials between 1955 and 2012, and Leucht et al. (2017) included 167 trials between 1955 and 2016. According to the names of the authors, publication year and the description of the original study, there were 77 studies that were included in both the 2013 and 2017 meta-analyses. The number may not be totally accurate, because Leucht et al. (2013) cites only 203 of the 212 trials because some publications reported on two or more studies. The original articles of the meta-analyses were read and the inclusion and exclusion criteria for the studies were collected. At this point, the studies that we could not access full text via the library of the University of Oulu were ruled out. Also, studies that could not be compared to NFBC1966, for example, studies considering only first onset of psychosis, were excluded. The studies and their inclusion and exclusion criteria were systematically collected from newest study to oldest until the most common ones had repeated themselves and saturated to stand out (until the year 2010). The total amount of original studies was 22, which is around 7 per cent of the total amount of studies included in Leucht et al. 2013 and 2017.

STATISTICAL METHODS

In cross-tabulations, percentages and Chi-Square tests (Pearson Chi-Square and Fisher's Exact test) were used to evaluate findings. The mean, median, standard deviation and range were used to describe continuous variables, and statistical differences were tested with the Mann-Whitney U test. Also, cumulative hospital treatment days (from national Care Register of Health Care) were analysed in both included and excluded groups using the same inclusion and exclusion criteria. IBM SPSS Statistics version 27 was used for the analyses.

RESULTS

MOST COMMON INCLUSION AND EXCLUSION CRITERIA IN THE CLINICAL TRIALS OF ANTIPSYCHOTICS

The 22 original studies were read systematically, tabulating all inclusion and exclusion criteria in the articles themselves or in the attachments. Due to the individual lexical formulation of the criteria in each study, differently worded but with the same meaning, criteria were combined so they retained their representativeness. The most often used inclusion and exclusion criteria were tabulated as seen in *Table 1*. Inclusion criteria often held diagnostic instruments (for example, PANSS and CGI) to map out the severity of the disease and symptoms and whether the study included inpatients or outpatients. Exclusion criteria often held restrictions on the antipsychotics individuals had been using earlier, how the individual's disease had reacted to earlier treatments and comorbidities.

Positive and Negative Syndrome Scale (PANSS)

Positive and Negative Syndrome Scale (PANSS) is a scale used to evaluate the severity of symptoms of individuals with psychosis. The PANSS score ranges from 30 to a maximum of 210 points[12]. In any form, PANSS was mentioned in 19 original studies. The score used to include and exclude individuals ranged from 42 to a maximum of 120 points, most commonly around 70 to 80 points. In 11 of the 22 original studies, the authors also required at least 4 points in at least two items in the positive subscale of the PANSS. Three of the original studies, which did not use PANSS as inclusion criteria, used Brief Psychiatric Rating Scale (BPRS) instead of PANSS.

Table 1. Most common inclusion and exclusion criteria in the original studies of Leucht et al. meta-analyses (13, 14)

Original study	PANNS as inclusion criteria	CGI ≥4 as inclusion criteria	Hospitalization as inclusion criteria	History of poor response to antipsychotics and earlier antipsychotic treatment	Other psychiatric diseases	Major somatic diseases
Correl et al. 2016	no	no	yes	no	excluded	No
Kinoshita et al. 2016	total ≥60 + pos. subscale criteria	yes	yes	excluded	no	No
Liebermann et al. 2016	no	no	no	excluded	excluded	excluded
Litman et al. 2016	total ≥70	yes	no	excluded	excluded	No
Loebel et al. 2016.	total ≥80 + pos. subscale criteria	no	yes	no	excluded	no
Correl et al. 2015	no	yes	yes	no	excluded	no
Kane et al. 2015	no	yes	yes	no	excluded	no
Durgam et al. 2014	total 80-120 + pos. subscale criteria	yes	yes	excluded	excluded	no
Bugarski-Kriola et al. 2014	total 80-120 + pos. subscale criteria	yes	yes	excluded	no	no
Downing et al. 2014	no	yes	yes	excluded	excluded	excluded
Litmann et al. 2014	total ≥70	no	no	excluded	excluded	no
Shen et al. 2014	total 70-120 + pos. subscale criteria	yes	yes	excluded	excluded	no
Egen et al. 2013	total ≥70 + pos. subscale criteria	no	no	excluded	excluded	excluded
Loebel et al. 2013	total ≥80 + pos. subscale criteria	yes	yes	no	no	no
Nasrallah et al. 2013	total ≥80 + pos. subscale criteria	yes	yes	excluded	excluded	excluded

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Original study	PANNS as inclusion criteria	CGI ≥4 as inclusion criteria	Hospitalization as inclusion criteria	History of poor response to antipsychotics and earlier antipsychotic treatment	Other psychiatric diseases	Major somatic diseases
Ogasa et al. 2012	total ≥42 + pos. subscale criteria	yes	yes	excluded	excluded	excluded
Schmid et al. 2012	total 60-120	yes	yes	excluded	excluded	excluded
Coppola et al. 2011	total 70-120	yes	yes	excluded	excluded	excluded
Ghaleiha et al. 2011	total ≥60	yes	yes	excluded	excluded	excluded
Kinon et al. 2011	no	yes	yes	excluded	no	excluded
Meltzer et al. 2011	total ≥80 + pos. subscale criteria	yes	yes	excluded	no	no
Kane et al. 2010	total ≥60	yes	yes	no	excluded	excluded

Clinical Global Impression Scale (CGI)

Clinical Global Impression Scale (CGI) is a 7-point scale to measure illnesses severity ranging from "not mentally ill" to "among the most severely ill". CGI was mentioned in 13 of 22 original studies with scores restricted to at least or greater than 4 in all of them, meaning the individuals who were at least moderately ill. There was no mention of the maximum CGI score in the original studies.

Hospitalization

As well as hospitalization, acute exacerbation was a common inclusion criterion in the original studies, in fact, it was mentioned in 20 of the 22 original studies. Because of the nature of the NFBC1966, acute exacerbation could not be used as a variable and was excluded from the collected inclusion and exclusion criteria of the original studies. However, as a common guideline for the treatment of acute exacerbation of schizophrenia, hospitalization often follows acute exacerbation to manage and control relapsed disease and the possible changes in patients' use of antipsychotics. 18 of the 22 original studies mention hospitalization as an inclusion criterion. Six of the original studies were more specific on the length of the hospitalization and four of the studies were completed with the patients being outpatients.

History of poor response to antipsychotics and earlier antipsychotic treatment

Due to individual vocabulary in the original studies, the combined "history of poor response to antipsychotics" criteria, consists of often mentioned "must have history of positive response to antipsychotics" in any form, diagnostic criteria of treatment-resistant schizophrenia (at least 2 different antipsychotics with adequate dosage and time) and the plain use of clozapine. In some way, history of poor response to antipsychotics is mentioned in 12 of the 22 original studies.

In total, eight of the original studies had restricted the use of certain antipsychotics before the trial with or without the history of poor response mentioned. Most commonly the case was depot antipsychotics during a certain timeline before the baseline. Break from the depot antipsychotics was mentioned as an inclusion criterion in four original studies and the break required before the baseline or the study ranged from 1 cycle of mentioned depot antipsychotics to 120 days.

Other psychiatric disorders

Psychiatric DSM-IV Axis I diagnosis other than schizophrenia was mentioned as an exclusion criterion in 17 of the 22 original studies. Nine of the studies excluded all diagnoses other than schizophrenia in the Axis I, three ruled out schizoaffective disorder, three ruled out major depression and two ruled out bipolar disorders.

DSMV-IV Axis I also contains diagnoses for substance abuse. In 13 original studies, substance abuse and/or dependence is mentioned as its own exclusion criteria. Six of the original studies do not mention any specific timeline, 5 studies exclude participants for substance abuse within 180 days before trial and 2 for 3 months before screening.

Somatic diseases

Major somatic diseases are characterized in some of the original studies as acute, unstable or untreated somatic diseases. Eight of the 22 original studies excluded individuals with any significant medical condition other than schizophrenia. Also, three of the 22 studies excluded participants with clinically significant abnormal laboratory values.

Chronic diseases of the central nervous system were mentioned in 10 of the 22 original studies. Two of these studies excluded any chronic central nervous system disease, but, for example, dementia, seizures and epilepsy were specifically mentioned

SELECTED INCLUSION AND EXCLUSION CRITERIA FROM THE ORIGINAL STUDIES IN THE NFBC1966 34-YEAR FOLLOW-UP

Positive and negative syndrome scale (PANSS)

Total PANSS score was available from 54 participants with a mean of 55.2 and a median of 50.1, ranging from a minimum of 30 to a maximum of 122. Altogether, 17 participants (31.5 per cent) had a total PANSS score of at least 60 and 11 participants (20.4 per cent) had a PANSS total of at least 60 with at least moderate severity in two or more of the positive symptoms. When total PANSS is restricted to at least 70, 10 participants (18.5 per cent) would be included, and when at least two moderate positive symptoms are counted in, seven participants (13.0 per cent) would be included.

Positive PANSS scores were also evaluated from the 54 participants. The mean was 13.70 (SD 5.19) ranging from 7 to 24 with a median of 13.5.

Table 2. The number of included participants by different Positive and Negative Syndrome (PANSS) inclusion criteria in the population of NFBC1966 34-year follow-up (N=54)

PANSS as an inclusion criterion 34y	N (%)
Total PANSS at least 60	17 (31.5)
Total PANSS at least 60 and at least 2 positive symptoms at least moderate severity	11 (20.4)
Total PANSS at least 70	10 (18.5)
Total PANSS at least 70 and at least 2 positive symptoms at least moderate severity	7 (13.0)

Clinical Global Impression Scale (CGI)

Clinical Global Impression Scale is available from a total of 57 participants in NFBC1966. Altogether, 51 participants (89.5 per cent) had a CGI score of at least moderate severity (CGI score of at least four).

Hospitalization

Because of the nature of the NFBC1966, there is no data from acute exacerbation of the participants with schizophrenia. However, there is cumulative data on days spent in hospital treatment which may indirectly suggest the commonness of both acute exacerbation and hospitalization. The cumulative hospital treatment days were collected from inpatients in the timeline 1.1.2000 to 31.12.2009.

History of poor response to antipsychotics and earlier antipsychotic treatment

Treatment resistant is considered in the NFBC1966 to be the use of clozapine or the use of at least two different antipsychotics with the dose of 600 chlorpromazine (CPZ). At the 34-year follow-up, 13 of the 56 participants (23.2 per cent) with available medical therapy history were considered treatment resistant at some point of their disease.

Other psychiatric diseases

During the 34-year follow-up, 6 of the 57 participants (10.5 per cent) had a psychiatric diagnosis other than schizophrenia. Also, 5 of the 57 participants (8.8 per cent) had a current substance abuse diagnosis.

Somatic diseases

In the 34-year follow-up of NFBC1966, 5 of the 55 total (9.1 per cent) participants were considered to have a major somatic disorder.

INCLUSION AND EXCLUSION CRITERIA OF THE ORIGINAL STUDIES COMPARED WITH THE POPULATION OF NFBC1966

In this study, we aimed to compare the population of the NFBC1966 with the population used in antipsychotic trials. After searching through inclusion and the exclusion criteria of the 22 original studies, we managed to make an estimated combination of the criteria used in antipsychotic trials. This combination includes PANSS as inclusion criteria set on different scores according to the commonness in the original studies. The combination uses CGI, treatment-resistant schizophrenia (TRS), current substance abuse and major somatic diseases as exclusion criteria. Hospitalization was not included, because of the longitudinal nature of the NFBC1966.

Combined exclusion criteria in NFBC1966 in the 34-year follow-up

Combined exclusion criteria consist of CGI less than moderate, individuals with treatment-resistant schizophrenia, current substance abuse or major somatic disorder. Twenty-four of the 57 individuals (42.1 per cent) would be excluded, and the remaining 33 individuals could be included depending on their PANSS score. PANSS was then accounted to the combined exclusion criteria in different scales which appeared the most often during the collection of the exclusion criteria of the original studies.

When comparing the combined inclusion and exclusion criteria to the inclusion criteria shown in *Table 2*, three additional participants would be excluded by the combined exclusion criteria in the group who had a PANSS total score of at least 60, two in the group with a PANSS total score at least 60 and the positive subscale counted in, two in the group with PANSS total at least 70, and one participant would be excluded in the group with total PANSS at least 70 and the positive subscale counted in.

For the individuals who would be excluded by the combination criteria, the mean for hospital treatment days from 1.1.2000 to 31.12.2009 caused by any psychosis was 164.88 with a standard deviation of 250.21 (N=43). Individuals who would be included had a mean of 30.86 days with a standard deviation of 44.55 (N=14). There was a statistically significant difference between the included and excluded groups in the Mann-Whitney U test (p-value 0.041).

Table 3. Different PANSS criteria with combined exclusion criteria (CGI less than moderate, individuals with treatment-resistant schizophrenia, current substance abuse, or major somatic disorder) of the original studies in NFBC1966 34-year follow-up
PANSS = Positive and Negative Scale

Combined exclusion criteria and different PANSS criteria	Included (%)	Excluded (%)	Total (%)
Total PANSS at least 60	14 (24.6%)	43 (75.4%)	57 (100%)
Total PANSS at least 60 and at least two moderate symptoms on positive subscale	9 (15.8%)	48 (84.2%)	57 (100%)
Total PANSS at least 70	8 (14.0%)	49 (86.0%)	57 (100%)
Total PANSS at least 70 and at least moderate symptoms on positive subscale	6 (10.5)	49 (89.5%)	57 (100%)

Table 4. Cumulative hospital treatment days caused by any psychosis from 1.1.2000 to 31.12.2009 in NFBC1996 individuals with schizophrenia divided into inclusion and exclusion groups by combination criteria of PANNS at least 60, CGI at least 4, and exclusion criteria of TRS, current substance abuse, other psychiatric and major somatic diseases

Combination criteria		Any psychosis hospital treatment days
Excluded	Mean	164.88
	SD	250.21
	N	43
Included	Mean	30,86
	SD	44.55
	N	14
Total	Mean	131.96
	SD	225.40
	N	57

Combined exclusion criteria in NFBC1966 in the 43-year follow up

NFBC1966 is longitudinal research, and the participants that attended the 34-year follow-up in the years 1999 to 2001 were also asked to attend the 43-year follow-up during the years 2008 to 2010. There had been some loss of participants, which affects the data based on the voluntary attending for the research. There is data from 36 participants who were evaluated in both the 34-year follow-up and in the 43-year follow-up.

Using the same combined exclusion criteria, at the 43-year follow-up, 20 individuals of 36 available participants (55.6 per cent) could be included. In this population, total PANSS had a mean of 72.5 and a median of 72 ranging from 30 to 130. With the individuals who would be excluded, the total PANSS had a mean of 83.4 and a median of 90.5 ranging from 39 to 131.

When using PANSS >70 as an inclusion criterion with the combined exclusion criteria, 10 participants of the 36 individuals (27.8 per cent) could be included. Using Pearson Chi-Square, there was no statistically significant difference between the groups (p=0.453). When the PANSS total was divided into groups >60 and 60 or lower, the group size of the participants, who would have been excluded and had a PANSS total of 60 or lower, was so small that the analysis prevented the use of an exact number of individuals because of restriction of privacy. However, using Fisher's Exact Test, there was no statistical significance in the difference between the groups of PANSS total >60 and 60 or lower (p=0.718).

Comparing the inclusion and exclusion criteria results between 34-year follow-up and 43-year follow-up

Because the unavailable data of 43-year follow-up group divided by total PANSS >60 and 60 or less, we chose the cutting point of groups as PANSS at least 70. Participants in the 34-year follow-up, who had PANSS total score of at least 70 were included and exclusions were made with the same combination criteria which were used earlier, which were analysed in the 43-year follow-up as seen in *Table 5*.

Table 5. Combination criteria (CGI <4, TRS, current substance abuse, and major somatic diseases), in the 43-year follow-up population

Excluded by combination criteria									
Outcome at 43 years	**Yes**			**No**			**Total**		
	N	**Mean (SD)**	**Median**	**N**	**Mean (SD)**	**Median**	**N**	**Mean (SD)**	**Median**
PANSS total score	16	83.44 (28.58)	90.50	20	72.55 (25.61)	72.00	36	77.39 (27.14)	75.50
PANSS positive symptoms score	16	18.50 (7.68)	18.50	20	15.10 (5.57)	16.50	36	16.61 (6.71)	17.00
SOFAS	16	44.69 (18.64)	34.50	20	49.10 (13.33)	47.00	36	47.14 (15.82)	43.50

Table 6. Participants were evaluated during the 34-year follow-up and grouped with the inclusion and exclusion criteria of the original studies compared with their evaluation in the 43-year follow-up

PANSS at least 70 and combination exclusion criteria in 34y		PANSS total in 43y	PANSS positive symptoms score in 43y	SOFAS in 43y
Excluded	Mean	75.84	17.00	48.32
	Median	74.00	17.00	45.00
	N	31	31	31
	Standard deviation	27.54	7.06	16.160
Included	Mean	87.00	14.20	39.80
	Median	79.00	16.00	37.00
	N	5	5	5
	Standard deviation	24.92	3.42	12.40
Total	Mean	77.39	16.61	47.14
	Median	75.50	17.00	43.50
	N	36	36	36
	Standard deviation	27.14	6.712	15.82

In the follow-up of both excluded and included groups in the 34-year follow-up, there was no statistically significant difference (Mann-Whitney U test) in the distribution of PANSS, positive or negative score or SOFAS in the 34-year follow-up groups of the combination criteria (p-value ranging from 0.325 to 0.396). The analysis was the same when PANSS score >70 was removed from the combination criteria.

DISCUSSION

Variation between clinical antipsychotic samples and natural population-based samples is caused by inclusion and exclusion criteria and the overall homogeneity of the sample, which is needed in RCTs. However, in the clinical world, patients are different, and heterogeneity is normal. The differences between our samples are quite significant. Depending on how strict the criteria for including and excluding individuals were used, 75.4 to 89.5 per cent of the NFBC1966 would not be included in clinical antipsychotic trials, and the results of the trials would not be necessarily generalizable to the NFBC sample. However, the statistical analyses showed no statistically significant difference between the included and excluded groups when only the inclusion and exclusion variables were compared. A statistically significant difference was found in long-term outcomes between the included and excluded groups. Taipale et al. (2022) estimated that RCTs may represent only about a fifth of the individuals with schizophrenia spectrum disorders in a population-based cohort with a total of 20 060 individuals with schizophrenia. Our findings follow the estimate on a smaller scale. However, in Taipale et al. [15] they simply used exclusion criteria to compare individuals, and in our study, we also used factors that are

used as inclusion criteria in clinical trials. Taipale et al. were more specific and went further in the identification of the exclusion criteria than we did in our study, and in our study, the criteria for exclusion had much weight in PANSS symptoms. The end results in our study and in Taipale et al. were in the same range but for different reasons.

The reason for the difference between the RCTs population and population-based data can probably be divided into two. First is the selection of the RCTs population to maximize the possibility of efficacy while the NFBC1966 population is natural and unselected. The second reason is that most of the participants in NFBC1966 were currently outpatients without acute exacerbation, while the individuals in the collected RCTs were included during the acute exacerbation of the disease, which has an effect, especially in PANSS scores. There would be a benefit in examining cohort studies as well, with RCTs of antipsychotics used for relapse prevention to map out further differences between selected and unselected individuals with schizophrenia. However, in the clinical mind, our finding is still notable. Both groups are treated with the same medicines (with different dosages), but the findings based on the use of those medicines are collected with acutely more severely ill individuals with fewer factors that may affect the outcome of treatment. There is not too much research on antipsychotics and their outcomes with unselected participants and the adverse effects of antipsychotics in years-long follow-ups. Our findings let us guess that there could be major differences in both if they were later studied.

During the years of NFBC1966 schizophrenia research, there have been studies informing the outcomes of individuals with schizophrenia. In Lauronen et al. [16], they used PANSS positive symptoms as a criterion for outcome. As a part of describing poor clinical outcome, an individual should have had more than one moderate positive symptom counting delusions, conceptual disorganization and hallucinations. In the original studies' inclusion criteria collected for this study, PANSS with at least two moderate positive symptoms was often mentioned. As a naturalistic setup (NFBC1966) and the fact that these individuals already had started treatment, this group included with the criteria of at least two moderate positive symptoms would automatically be a part of the poor outcome group depending on if the two moderate ones consisted of the three mentioned above. However, when only the PANSS total score (restricted to at least 70) was noted in the 34-year follow-up, when analysed, the same individuals were again in the 43-year follow-up, the included individuals in the 34-year follow-up had fewer positive symptoms score in the 43-year follow-up than the individuals excluded. This may indirectly suggest that the included individuals in the 34-year follow-up may have had a better prognosis than the individuals excluded, however, more research would be needed to confirm this. An important aspect for following studies would be to study differences in mortality rates between the included and excluded groups.

In the clinical world, the difference in outcomes between clinical antipsychotic trials and in the real-world population has to be noted. If the clinical antipsychotic trials represent only around 25 per cent of the clinical world population as our findings suggest, the same outcomes cannot be expected in both groups. This further highlights the need for systematic medication management for individuals with schizophrenia, as the same antipsychotics are used as a long-term treatment to prevent relapses in schizophrenia.

LIMITATIONS AND STRENGTHS

The main limitation of this study is the rather small size of the NFBC1966 sample and loss of the participants during the follow-up. NFBC1966 is a naturalistic study of individuals expected to be born in 1966 and the number of individuals with a schizophrenia diagnosis is restricted by this. In the 34-year follow-up, there were 57 individuals with a schizophrenia diagnosis, and 36 of them were evaluated again in the 43-year follow-up. The loss of participants has been studied in the NFBC1966. Haapea et al. [17] studied the NFBC1966 population, examining participants who had a lifetime diagnosis of psychosis. The non-participants in later follow-ups were more often patients with schizophrenia and had more psychiatric hospitalizations with more positive symptoms.

NFBC1966 consists of individuals with schizophrenia at many different stages of the disease. If we would simply study how many of these individuals could be included in clinical antipsychotic trials, this could be seen as a limitation. However, as we have been studying the representativeness of the antipsychotic trials' population compared to the population-based sample, this makes a notable advantage in the NFBC1966 population. In this type of naturalistically set up sample, we can see how many different comorbidities and other factors that may affect the treatment of schizophrenia there are in a real-life clinical population.

Another notable strength in our sample is the almost exceptionally long follow-up with the individuals with schizophrenia. As mentioned before, according to Leucht

et al. [6] in the meta-analysis of 65 antipsychotic RCTs, the median duration of follow-up was 26 weeks and there were only a few 3-year follow-ups. In this study, we used data from the 34-year follow-up, which was collected during the years 1999 to 2001, and the 43-year follow-up, which was collected during the years 2008 to 2010.

CONCLUSION

Participants in clinical trials seem to have higher PANSS scores, which seems to be the greatest simple factor difference between the populations. It is also notable that the combined exclusion criteria excludes 42.1 per cent of the population in our sample. When both the PANSS score and combined exclusion criteria were accounted for, depending on the strictness of PANSS criteria, 10.5 to 24.6 per cent of the population in the NFBC1966 34-year follow-up could be included in clinical antipsychotic trials. It seems that the NFBC1966 population is both less severely ill in the order of PANSS and also has more other factors that may affect the treatment of schizophrenia with antipsychotics. However, in the analyses done, there is no statistically significant difference between the included and excluded groups in this data.

The hypothesis for this study was that individuals in NFBC1966 are more severely ill and have more comorbidities than the individuals in clinical antipsychotic trials. This proved to be half true. Around one-third of the individuals could be excluded by factors not directly depending on schizophrenia. However, PANSS was the most common simple factor why the individuals would not be included in clinical antipsychotic trials. This may partly be because of the setup of NFBC1966. There is not any guarantee that the individuals in NFBC1966 happen to have an acute exacerbation during the follow-up, as often mentioned as an inclusion criterion. This might lead to lower scores in PANSS with the individuals of NFBC1966. However, it is also notable that the individuals excluded via combined exclusion criteria had statistically significantly more hospital treatment days than the individuals included. This might suggest that even though individuals in NFBC1966 had lower PANSS scores, the comorbidities made the management of schizophrenia more difficult in the excluded population and individuals more severely ill in other ways than simply viewed through the PANSS score.

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