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Mortality and non-use of antipsychotic drugs after acute admission in schizophrenia: A prospective total-cohort study

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ABSTRACT

Background: In society at large, it is debated whether use of antipsychotic drugs is associated with increased or decreased mortality among patients with schizophrenia. Large register studies have demonstrated an increased mortality risk associated with non-use of antipsychotic drugs, but prospective studies are missing.
Aims: To investigate the association between mortality and non-use of antipsychotics in patients with schizophrenia.
Method: An open cohort study included and followed all patients with a discharge-diagnosis of schizophrenia consecutively admitted to a psychiatric acute unit at Haukeland University Hospital, Bergen, Norway during a 10 year period ($n = 696$). Cox multiple regression analyses were conducted with use of antipsychotic drugs as a time dependent variable, and periods of use and non-use were compared within individual patients. Adjustments were made for gender, age at index admission, number of acute psychiatric hospital admissions, excessive use of alcohol and illicit substances and use of benzodiazepines and antidepressants.
Results: A total of 68 (9.8%) deaths were registered during follow-up. Of these, 40 (59%) had natural causes, whereas 26 (38%) had unnatural causes. Non-use of antipsychotics was associated with 2.15 ($p = .01$, CI: 1.24–3.72) times higher mortality risk compared to use of antipsychotics. The difference in mortality risk between use and non-use of antipsychotic drugs was age dependent, with the largest risk difference in young patients.
Conclusions: Non-use of antipsychotic drugs was associated with twofold increased mortality risk in patients with schizophrenia.

1. Introduction

Schizophrenia is a serious mental disorder with a prevalence just below 1% (Janoutova et al., 2016; Kahn et al., 2015), and is associated with severe problems in many areas of life, including inability to work, social disability and drug abuse (Tandon et al., 2009). Antipsychotic drugs remain a cornerstone in treatment guidelines worldwide (Hasan et al., 2013; Lally and MacCabe, 2015), but treatment can be challenging, reflected by non-adherence rates as high as 40–75% (Lacro et al., 2002; Leucht and Heres, 2006). Recently, patient organizations have advocated for the need of psychosis treatment without antipsychotic drugs. As a result, «medication-free» treatment services have been established within the Norwegian public health care system. Although some studies on psychosocial interventions for schizophrenia without the use of antipsychotic drugs have been conducted, the evidence is generally of low quality (Cooper et al., 2020). Hence, there is an urgent need to evaluate the consequences of choosing not to use antipsychotic drugs.

The mortality risk among patients with schizophrenia is considerably higher than in the general population (Heiberg et al., 2018; Nome and

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Holsten, 2012), with reduced life expectancy reported in the range of 11 to 20 years (Hjorthoj et al., 2017; Laursen et al., 2013). Increased risk of premature death from both natural and unnatural causes have been found, with cardiovascular disease (CVD), respiratory disease and suicide being major causes (Olfson et al., 2015). Although reasons are likely to be multifactorial, spanning from genetic vulnerability to lifestyle factors (Andreassen et al., 2013), it is evident that common adverse effects of antipsychotic drugs such as obesity, dyslipidaemia, and diabetes contribute to the increased mortality risk (Mackin et al., 2007). Paradoxically, however, a great number of studies find a decreased risk of death associated with the use of antipsychotics compared to non-use, as demonstrated in a recent meta-analysis (Vermeulen et al., 2017). Methodological shortcomings of the studies, particularly related to their retrospective designs (Chen et al., 2019; Vermeulen et al., 2017), make them vulnerable to incomplete reporting of data and inadequate control for potentially confounding variables (De Hert et al., 2010; Thygesen and Ersboll, 2014). There is thus a need of prospective studies with predefined research questions and targeted data acquisition that account for crucial factors such as non-adherence and the high drug discontinuation rates. Accordingly, we aimed to investigate how use versus non-use of antipsychotic drugs is associated with mortality in a total-cohort of patients with schizophrenia consecutively admitted to a large psychiatry acute unit.

2. Material and methods

2.1. Sample

The study was conducted at the Division of Psychiatry, Haukeland University Hospital, Bergen, Norway. Haukeland University Hospital receives approximately 95% of all patients in need of acute psychiatric hospital admission from a catchment area of about 400,000 inhabitants. All patients consecutively admitted to the Psychiatry Acute Unit between May 1st 2005 and June 15th 2014, who met the criteria of a discharge ICD-10 (https://icd.who.int/browse10/2019/en) diagnosis of schizophrenia (F 20.0-F 20.9) were eligible for inclusion. As presented in Fig. 1, a total of 772 eligible patients were admitted during the 10-year period. Of these, 76 patients were excluded due to lack of information about the use of antipsychotic drugs after discharge. Accordingly, 696 patients were included in the final sample.

2.2. Procedure

Patients with a diagnosis of schizophrenia were included at the first acute admission during the study period, hereby named the index admission. Clinicians who were involved in the assessment of patients at admission underwent training in the rating scales used. The patients were followed from the first day of the index-admission and until May 1st 2015 or the date of death or censoring. Patients were censored when they moved out of the hospital catchment area ($n = 48$), or if they were lost to follow-up for other reasons ($n = 142$). If no information about the patients use or no-use of antipsychotic medication was available, the patient was censored after the last day of information. Data, including periods of use and periods of non-use of antipsychotic drugs, were collected from the medical records for each patient both during and in-between any hospital admissions. The study benefits from the complete and transparent public mental health system in Norway, which makes it possible to follow individual patients through the follow-up at different levels of care. Data on drug prescriptions and adherence during the periods in-between admissions were obtained retrospectively from the patients' medical records. Drug adherence in-between admissions was evaluated based on all available information from the patients, families, mental health care records and serum level measurements of antipsychotic medications when available. To avoid discrepancy in how information was obtained and registered, M.F.S. and M.K. did all the data extraction. Any questions regarding registrations were logged and discussed in the researcher team. In order to avoid overestimation of drug discontinuation, we allowed for periods of discontinuation lasting up to two weeks without registering a termination, as long as the drug was restarted. Data on death were obtained by linking the patients' 11-digit identity number to information from the Norwegian Cause of Death Registry (conducted November 14th 2016). Dates for moving out of the hospital's catchment area were recorded from the medical records.

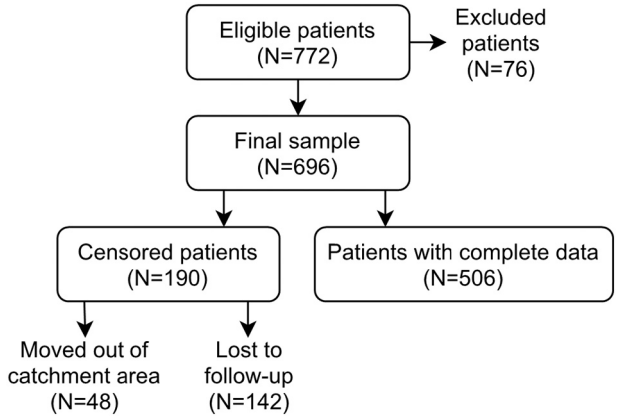

Fig. 1. Flow of patients through the study.

2.3. Measurements

To reflect treatment periods with and without antipsychotic drugs, we recorded the use of as a time dependent variable, meaning that the variable may change for an individual patient during the follow-up period. The antipsychotic drug-variable was coded 1 for the time period a patient used antipsychotic drugs, and 0 otherwise. The term "non-use" of antipsychotic drugs included both patient non-adherence and clinician-guided drug discontinuation. Medications were classified according to the Anatomical Therapeutic Chemical- (ATC) system, and only antipsychotics primarily given on the indication of psychosis were counted. Included antipsychotic drugs were amisulpride, aripiprazole, clozapine, flupentixol, haloperidol, olanzapine, paliperidone, perphenazine, pimozide, quetiapine, risperidone, sertindole, ziprasidone and zuclopenthixol. The use of alcohol and illicit substances were measured using the Alcohol Use Scale (AUS) and the Drug Use Scale (DUS), single-item clinician-rated indexes of alcohol and drug abuse (Drake et al., 1996). Use is measured on a 5-point scale from no problems to extremely severe problems. In accordance with previous literature, a score of 3 or higher was classified as excessive use (Van Wormer, 2010). For patients with two or more admissions during the study period, the highest given score on AUS and DUS was used in the analyses. When values were missing ($n = 30$), the AUS and DUS score were set to 0. Acute psychiatric hospital admissions and the use of benzodiazepines and antidepressants were recorded as time dependent variables. The variables were coded 1 if admitted to hospital or when benzodiazepines and antidepressants where used, and 0 otherwise. Acute psychiatric hospital admissions included inpatient treatment periods at Community Mental Health Centres (CMCH) directly following an acute admission.

2.4. Statistics

Cox regression models were used to analyse the effect of antipsychotic drugs use on mortality, which was the primary endpoint of the study. In order to test the robustness of the results, both univariate and multivariate analyses were conducted. The models compare the continuous mortality risk of use versus non-use of antipsychotic drugs. The multivariate model adjusted for gender, age at index admission, acute psychiatric hospital admission, excessive use of alcohol and illicit substances and use of benzodiazepines and antidepressants. Sensitivity

analyses including an interaction term between use of antipsychotic drugs and age were undertaken, as well as analyses in separate age categories. The statistical software *R version 4.0.2* (https://www.r-project.org/) and the package *survival* were used for the statistical analyses. The cox-proportional hazard assumption was checked using the cox.zph() function.

2.5. Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Norwegian Social Science Data Service, the Norwegian Directorate of Health Care and the Regional Committee for Medical Research Ethics (Approval number REK 46004). Use of patient information without informed consent was authorized by these instances.

3. Results

Clinical and sociodemographic characteristics are presented in Table 1. On average, patients were followed for 4.6 years (SD = 3.1). The median number of admissions were 0.65 per year. Throughout the study period, 142 (20.4%) patients were censored due to lack of information about their use of antipsychotic medications. During follow-up, 48 patients (6.9%) were censored because they moved out of the hospital's catchment area, and 68 patients (9.8%) died. A total of 40 patients (58.8%) died from natural causes and 26 (38.2%) died due to unnatural causes. The most frequent causes of death were cardiovascular disease and accidental poisoning for natural and unnatural death, respectively. Causes and age at time of death are presented in Table 2.

Results of the Cox multivariate and univariate analyses are presented in Table 3. In the univariate analysis, there was a significant positive association between mortality and non-use of antipsychotic medications (*Adjusted hazard ratio (AHR) = 2.31, p = .002 CI: 1.36–3.94*), meaning that the risk of death at any timepoint is 2.31 times higher when antipsychotic drugs are not used compared to periods with antipsychotic drug use. There was also a positive association between mortality and age (*AHR = 1.05, p < .001, CI: 1.03–1.06*), meaning that mortality risk increases by 5% per year. No significant associations were found between mortality and gender, hospitalization, excessive use of alcohol, excessive use of illicit substances, use of benzodiazepines and use of antidepressants. Results of the multivariate analysis were not different from those in the univariate analyses, except gender, where a significant negative association was found between mortality and female gender in the multivariate analysis (*AHR = 0.50, p = .01, CI: 0.30–0.87*).

Results of the sensitivity analysis including the interaction term between age and use of antipsychotic drugs are presented in Table 4. A significant negative association was found for the interaction effect between use of antipsychotic drugs and age (*AHR = 0.95, p = .01, CI: 0.92–0.99*). As the interaction term reflects a linear slope, this means that the difference in mortality risk between use and non-use of antipsychotic drugs decreases by 5% per year. Results of the sensitivity analysis were not different from those in the main analysis. The significant positive association between mortality and non-use of antipsychotic medications remained in the sensitivity analyses (*AHR = 2.88, p < .001, CI: 1.60–5.20*), the AHR estimate now referring to a patient at mean age (41.1 years). When the association between mortality and non-use of antipsychotics were investigated separately in different age categories, the direction for the interaction effect was supported, as the largest risk differences between use and non-use were found in the youngest patients. In the analyses for separate age categories, the strongest association between mortality and non-use of antipsychotic medications was found for patients under 30 years (*AHR = 3.54, p = .02, CI: 1.18–10.56*). For patients over 70 years, no significant association between mortality and non-use of antipsychotic drugs was found. Based on the interaction term, calculated AHR was 6.06 and 0.60 for a 25 year old and a 75 year old, respectively. Thus, the AHR estimate in the youngest age categories was smaller than that found by extrapolating the linear interaction term. Accordingly, the magnitude of the risk difference seemed to be overestimated by the interaction term in the

Table 1
Baseline characteristics of the sample ($n = 696$)[a].

	N	Percent
Gender		
Male	431	61.9%
Female	265	38.1%
Receiving social benefits at index admission ($n = 676$)	612	90.5%
Non-Norwegian ethnicity	85	12.2%
Highest completed education ($n = 617$)		
Primary school, 7–9 years	335	54.3%
Secondary school, 12 years	207	33.5%
University or college	75	12.2%
Previous treatment contact		
Outpatient care	41	5.9%
Inpatient care	620	89.1%
No previous treatment contact	35	5.0%
Schizophrenia diagnosis at discharge from index admission		
F20.0	533	76.6%
F20.1	50	7.2%
F20.2	6	1.0%
F20.3	40	5.7%
F20.4–9	67	9.6%
Comorbid alcohol or drug problem at index admission		
AUS score ≥ 3 ($n = 618$)	68	11.0%
DUS score ≥ 3 ($n = 625$)	93	14.9%
Comorbid ICD-10 diagnosis, F10.0-F19.9	97	13.9%

	Mean (range)	SD
Age at index admission	41.1 (16–92)	14.7

N = number.
SD = standard deviation.
AUS = Alcohol Use Scale.
DUS = Drug Use Scale.
ICD10 diagnoses:
F20.0 = paranoid schizophrenia.
F20.1 = hebephrenic schizophrenia.
F20.2 = catatonic schizophrenia.
F20.3 = undifferentiated schizophrenia.
F20.4–9 = post-schizophrenic depression, residual schizophrenia, simple schizophrenia, other schizophrenia and unspecified schizophrenia.
F10.0-F19.9 = mental and behavioral disorders due to psychoactive substance abuse.
[a] If values are missing, the total *n* is presented.

Table 2
Causes of mortality.

	N	Percent
Died during follow-up	68	9.8%[a]
Natural death	40	58.8%[b]
Neoplasms	7	10.3%[b]
Cardiovascular disease	18	27.9%[b]
Chronic lower respiratory disease	9	13.2%[b]
Others	6	7.4%[b]
Unnatural death	26	38.2%[b]
Suicide	9	13.2%[b]
Accidental poisoning	13	19.1%[b]
Other accidents	4	5.9%[b]
Unknown cause of death	2	2.9%[b]

	Mean (range)	SD
Age at time of death	51.3 (19–93)	17.8

[a] Percent of total ($n = 696$).
[b] Percent of deceased ($n = 68$).

Table 3
Predictors of death.

T	Multivariate analysis			Univariate analyses		
	AHR	95% CI	*P*-value	HR	95%CI	P-value
Age at index admission, per year	1.05	1.04–1.07	<.001	1.05	1.03–1.06	<.001
Gender (male gender = 1)	0.50	0.30–0.87	.01	0.68	0.40–1.15	.15
Non-use of antipsychotic drugs (use = 1)	2.15	1.24–3.72	.006	2.31	1.36–3.94	.002
Acute psychiatric hospital admission (no = 1)	1.37	0.71–2.65	.34	1.25	0.66–2.38	.49
Excessive use of alcohol[a] (no = 1)	0.87	0.44–1.74	.69	1.02	0.58–1.79	.94
Excessive use of illicit substances[b] (no = 1)	1.99	0.98–4.05	.06	1.19	0.69–2.07	.53
Use of benzodiazepines (no = 1)	1.27	0.68–2.35	.45	1.35	0.74–2.47	.33
Use of antidepressants (no = 1)	0.59	0.27–1.31	.20	0.48	0.22–1.05	.07

AHR = adjusted hazard ratio.
[a] AUS ≥ 3.
[b] DUS ≥ 3.

Table 4
Predictors of death: sensitivity analysis including interaction term between age and use of antipsychotic drugs.

T	Multivariate analysis		
	AHR	95% CI	P-value
Age at index admission, per year	1.07	1.05–1.09	<.001
Gender (male gender = 1)	0.49	0.28–0.85	.01
Non-use of antipsychotic drugs (use = 1)	2.88	1.60–5.20	<.001
Interaction between age and use of antipsychotic drugs	0.95	0.92.0.99	.01
Acute psychiatric hospital admission (no = 1)	1.50	0.77–2.89	.23
Excessive use of alcohol[a] (no = 1)	0.90	0.45–1.81	.77
Excessive use of illicit substances[b] (no = 1)	1.84	0.90–3.77	.09
Use of benzodiazepines (no = 1)	1.26	0.68–2.35	.46
Use of antidepressants (no = 1)	0.63	0.28–1.39	.25

AHR = adjusted hazard ratio.
[a] AUS ≥ 3.
[b] DUS ≥ 3.

youngest patients.

4. Discussion

In this cohort of acutely admitted patients with schizophrenia, non-use of antipsychotic drugs after discharge was associated with increased mortality risk. The risk difference between use and non-use of antipsychotic drugs was age dependent, with the largest risk difference in young patients. The association between mortality and use versus non-use of antipsychotic drugs was analysed in a time dependent manner, and we are not aware of similar studies conducted in a consecutively included total-cohort. As even the most severely ill patients were included, our sample is representative for patients with schizophrenia discharged from hospital after an acute admission.

It is generally assumed that common adverse effects of antipsychotic drugs such as obesity, dyslipidaemia, and diabetes mellitus contribute to premature mortality in schizophrenia (Mackin et al., 2007). Indeed, antipsychotics seem to increase the risk of myocardial infarction and cerebrovascular incidences (Correll et al., 2017; Yu et al., 2016). Rarely, antipsychotic drugs may cause malignant arrhythmias, myocarditis, thromboembolism and sudden cardiac death (Bellissima et al., 2018; Jonsson et al., 2018; Ray et al., 2009; Wu et al., 2015; Zhu et al., 2019). Some studies conducted in the era of first generation antipsychotic drugs have found an association between high exposure to antipsychotic drugs and increased mortality (Joukamaa et al., 2006; Waddington et al., 1998). Further, first generation antipsychotics, but not second generation drugs, were found to be associated with increased mortality risk in a health insurer database (Tenback et al., 2012). Different mortality risk between antipsychotic drug classes may contribute to some inconsistent findings in old versus more recent studies, reflecting temporal different patterns of antipsychotic drug use and dosing across decades. A study by Torniainen et al. (Torniainen et al., 2015) also reported higher risk of death in patients with higher exposure to antipsychotic drugs compared to patients with low or moderate exposure. Paradoxically, the highest risk of death was found in patients that do not use antipsychotic drugs, suggesting that poor life-style and reduced capacity for health promoting behaviour associated with untreated psychosis may outweigh the long-term adverse effects of antipsychotic drugs (Tiihonen et al., 2009).

Our results are in line with the study by Torniainen et al. (Torniainen et al., 2015) as well as a large number of studies concluding that use of antipsychotic drugs decreases the mortality risk (Baxter et al., 2016; Crump et al., 2013; Cullen et al., 2013; Taipale et al., 2018; Tiihonen et al., 2011; Tiihonen et al., 2009; Tiihonen et al., 2016; Tiihonen et al., 2006; Torniainen et al., 2015; Vermeulen et al., 2017). Completely in accordance with our findings, most of these studies report that non-use of antipsychotic drugs increases the mortality risk with a factor close to 2. Reasons are most likely multifactorial, but may include that patients with untreated psychosis have a higher risk of suicide (Aydin et al., 2019; Nielssen et al., 2012). Symptoms associated with psychosis, such as distorted perception of reality, disorganized thoughts, impulsivity and poor problem solving skills can compromise the patients' ability to perceive risks and protect themselves, and these patients are more likely to be involved in accidents and violent incidents (Teplin et al., 2005). Adding to this, studies have shown that CVD risk factors are not only associated with antipsychotic medications, but also with schizophrenia itself (Andreassen et al., 2013; Rajkumar et al., 2017). This association is extra unfortunate bearing in mind that patients with psychosis tend to seek medical care for somatic problems less often than the general population, and are likely to demonstrate poor understanding of physical illnesses and preventive behaviour (Kim et al., 2019; Swildens et al., 2016). Thus, dampening of psychosis may facilitate a healthier lifestyle and more active health care-seeking behaviour in case of emerging somatic symptoms. Antipsychotic drugs may as such contribute to decreased risk of premature natural death.

Moreover, the risk difference between use and non-use of antipsychotic drugs was age dependent. The largest difference in mortality risk between use and non-use of antipsychotic drugs was found in the youngest age group. In previous studies, the highest standardized mortality rates (SMR) have been found among the youngest patients with schizophrenia, with elderly patients having the lowest SMR (Piotrowski et al., 2017). Based on this, it may be plausible that any mortality risk-reducing effect of antipsychotic drugs is most pronounced in the youngest age group, and with limited effect among the elderly. Indeed, no difference in mortality risk between use and non-use of antipsychotic drugs in elderly patients was found in our study. Interestingly, a recent systematic review on short-term mortality of second-generation antipsychotics found no evidence of increased mortality, except in elderly patients (Schneider-Thoma et al., 2018). Theoretically, the substantially reduced life expectancy found in schizophrenia may lead to survival bias, meaning that those who live to reach a high age represents a healthier subgroup. Any secondary beneficial effect of psychosis-reduction on life style and health seeking behaviour may therefore be

less important in this sub-group, whereas long-term adverse antipsychotic drug effects have relatively larger impact on mortality risk.

Our results also indicate that gender is an important factor in regard to mortality. For women, the all-cause mortality risk was significantly lower compared to men (AHR = 0.5). Similar results are found in other studies in the field, where male gender has been associated with increased risk of both natural and unnatural death. Reasons for this gender differences are multifactorial, and studies have reported that cardiovascular mortality, lung cancer mortality and suicide are higher in men than in women (Olfson et al., 2015).

4.1. Limitations and strengths

Data collection such as ours will always involve some elements of subjectivity, but we have ensured transparent and rigorous methods of data collection by using defined algorithms in cases of doubt. In cases of uncertainty regarding the use of medications, the patients were censored. In the present study, the term "non-use" of antipsychotic drugs included both non- adherence and drug discontinuation guided by a clinician. We do not know how and to what extent non-adherence and sudden discontinuation of antipsychotic drugs may have affected our results. The mortality risk may be lower if the discontinuation of antipsychotic drugs is gradual under the supervision of a clinician. Poor drug adherence is not always discovered and described in the patients' medical records, and it is possible that some of the patients on oral medications had a poorer adherence than registered. If so, that would indicate that "use of antipsychotic drugs" actually is a mix of use and non-use. As such, the differences found for mortality may represent underestimations. In accordance with other studies in the field, we allowed for periods of discontinuation lasting up to two weeks without recording a termination, as long as the drug was restarted (Mullins et al., 2008; Sikka et al., 2005). This may also have caused an underestimation of the differences we found in mortality between use and non-use of antipsychotic drugs. Another limitation is the lack of information about the doses of the antipsychotic medications.

We did not have information about the patients' somatic diseases, body mass index, blood pressure, cholesterol or smoking habits, which all are potential risk factors of premature death. It has been suggested that smoking may reduce extrapyramidal side-effects induced by antipsychotic medication (Sagud et al., 2009). Therefore, it is possible that use of antipsychotic drugs is associated with more smoking than non-use. Antipsychotic drugs are also associated with increased risks of diabetes, obesity and dyslipidaemia (Liebzeit et al., 2001; Mackin et al., 2007; Stahl et al., 2009). Hence, as the burden of cardiovascular risk factors may be higher during use of antipsychotic drugs, the mortality difference attributed to use versus non-use of antipsychotic drugs may be underestimated.

As a rule of thumb, the number of outcome events per predictor variable should be 10 or more in Cox regression models (Vittinghoff and McCulloch, 2007). We used 8 predictor variables in the main analysis, and the number of outcome events (deaths) was 68. This results in 8.5 deaths per variable, which is not ideal from a statistical point of view. However, Vittinghoff et al. (Vittinghoff and McCulloch, 2007) concluded that 5–9 outcome events per variable are usually sufficient. Furthermore, results of univariate analyses were not different from those in the main analysis, except for gender. Gender was not significantly associated with mortality in the univariate analysis, probably due to higher mean age at time of index in women (44.1 years) than in men (39.3 years). Accordingly, there is little reason to assume that the results would be different with a lower number of predictor variables in the main analysis.

The large and comprehensive sample and the long follow-up time are major strengths of the present study. In average, patients were followed for 4.6 years, and the maximum follow-up time was 10 years. As use of patient information without informed consent was authorized, all patients with a discharge-diagnosis of schizophrenia consecutively admitted to a large psychiatry acute unit was included in this total-cohort. Hence, even the most severely ill patients, who would otherwise not be able to cooperate and consent, were included. Consequently, our sample is highly representative for patients with schizophrenia admitted to a psychiatric acute unit. As our sample includes *all* acutely admitted patients with schizophrenia, not only a selection, our study can be compared to nationwide register studies with larger sample sizes. However, it is important to emphasize that the majority of our participants had several relapses and readmissions. The median number of admissions were 0.65 per year, and our sample is therefore representative for the subgroup suffering from several relapses, but not necessarily for all patients with schizophrenia, and particularly not those without the need for inpatient treatment. Hence, clinical and demographical characteristics of our sample may differ from those of studies with less severely ill patients.

The reflection of the clinical reality where patients have periods on and off psychotropic drugs is another strength. Unlike most studies on mortality and use of antipsychotic drugs, we accounted for non-adherence and drug discontinuation, as well as important confounders such as use of alcohol, illicit substances, benzodiazepines and antidepressants. Accordingly, the present study is able to provide a good analysis of the association between antipsychotic drugs and death in patients with schizophrenia, and thus provide important information with regard to decision-making concerning use versus non-use of antipsychotic drugs for patients and their caretakers.

5. Conclusion

This study provides evidence that non-use of antipsychotic drugs is associated with more than twofold increased mortality risk in patients with schizophrenia. In the light of our findings, measures to optimise use of antipsychotic drugs should be strengthened and systematized. The increased mortality associated with non-use of antipsychotic drugs emphasizes the need for better psychoeducation, motivational work and tailored treatment that focuses on reduction of adverse effects.

CRediT authorship contribution statement

M.F.S drafted the manuscript and contributed to extraction of the data, study design, statistical analysis and interpretation of the results. C.B.J performed statistical analysis and contributed to study design and interpretation of the results. L.S.M. contributed to the study design, supervised the data collection of baseline-data and revised the manuscript. R.A.K. contributed to the study design and revised the manuscript. M.K. contributed to extraction of the data. L.M. contributed to the study design and revised the manuscript. E.J. revised the manuscript and contributed to study design and interpretation of the results. All authors have approved the final version of this work.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.07.009.

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