JAMDA 21 (2020) 1636–1642

JAMDA

journal homepage: www.jamda.com

Original Study

Antipsychotic Drugs and Hip Fracture: Associations Before and After the Initiation of Treatment

Jon Brännström MD *, Hugo Lövheim MD, PhD, Yngve Gustafson MD, PhD, Peter Nordström MD, PhD

Department of Community Medicine and Rehabilitation, Geriatric Medicine, Umeå University, Umeå, Sweden

Keywords:
Antipsychotic drugs
hip fracture
cohort study

A B S T R A C T

Objective: To study the association between antipsychotic drug treatment and hip fracture, before and after the initiation of treatment.
Design: Nationwide cohort study.
Setting and Participants: In this study based on several Swedish registers, all individuals age ≥65 years who filled prescriptions for antipsychotic drugs in 2007–2017 were matched 1:1 by sex and age with controls, resulting in a cohort of 255,274 individuals.
Measures: Associations between antipsychotic drug treatment and hip fracture were investigated using multivariable conditional logistic regression models and flexible parametric survival models for non-proportional hazards, starting 1 year before the first prescription was filled and extending to 1 year thereafter.
Results: The studied cohort had a mean age of 81.5 (standard deviation, 8.1) years; 152,890 (59.9%) individuals were women. Antipsychotic drug use was associated with an increased risk of hip fracture in all studied time frames, before and after the initiation of treatment. The risk was highest 16–30 days before the initiation of treatment (odds ratio 9.09; 95% confidence interval 7.00–11.81). The pattern was consistent in subgroup analyses of users of conventional and atypical antipsychotics, men and women, as well as in younger old and older old participants. The association with hip fracture was not influenced by antipsychotic drug dose.
Conclusions and Implications: The association between antipsychotic drug use and the risk of hip fracture was observed before the initiation of antipsychotic treatment. This finding suggests that factors other than exposure to antipsychotic drugs are responsible for the increased risk of hip fracture in the treatment group.

Antipsychotic drugs, although designed mainly for the treatment of schizophrenia, are often prescribed to older people with no primary psychotic disorder.[1,2] A common and controversial application is the use of antipsychotics for the management of neuropsychiatric symptoms among individuals with major neurocognitive disorders (NCD), such as delusions, hallucinations, aggression, and agitation.[3,4] Most geriatric researchers and physicians agree that antipsychotic drugs should be used only when other interventions have failed and that the treatment duration should be kept to a minimum.[5–7] This reasoning is based on the often limited efficacy of these drugs and the many observed adverse effects, including increased risks of mortality and stroke.[8–13] Still, in selected cases, antipsychotics could have important treatment effects; it is thus important that the risks are not exaggerated, to allow for fair weighting of treatment risks and benefits. Among the more serious adverse effects described is the increased risk of hip fracture, a commonly occurring incident in old age associated with high mortality and loss of function.[14] However, this increased risk associated with the use of antipsychotic drugs has been observed only in observational studies,[15,16] which have pronounced risks of different forms of bias. In particular, the difficulty of accounting fully for underlying disease that may increase the risk of fracture and the chance of being prescribed certain drugs may result in biased outcomes. In a recent study, we showed that the increased risk of hip fracture associated with antidepressant use was highest in the weeks before the drug was dispensed for the first time;[17] another study revealed the same pattern for

This study was supported by funds from the Swedish Research Council, Sweden and the Foundation for Medical Research in Skellefteå, Sweden, neither of which had no role in the study design, data collection, analysis, or interpretation, or writing of the manuscript.
The authors declare no conflicts of interest.
* Address correspondence to Jon Brännström, MD, Geriatric Medicine, Umeå University, SE-901 87 Umeå, Sweden.
E-mail address: jon.brannstrom@umu.se (J. Brännström).

https://doi.org/10.1016/j.jamda.2020.06.047

hypnotic use.[18] Hence, it remains to be proven that these and other psychotropic drugs actually increase the risk of fracture.

The aim of the current study was to examine the association between antipsychotic drug use and hip fracture, before and after the initiation of treatment, in a matched population-based nationwide Swedish cohort of individuals aged ≥65 years.

Methods

Data Sources

Four nationwide Swedish registers were used as data sources for this cohort study. Pharmaceutical data was collected from the Prescribed Drugs Register, which contains information on all drug prescriptions dispensed at Swedish pharmacies since July 1, 2005.[19] Data on the outcome, hip fracture, and comorbidities were retrieved from the National Patient Register, which contains records of all diagnoses established during inpatient care since 1987 and during specialist outpatient visits since 2001. The positive predictive value for hip fracture has been shown to be >95%.[20] Socioeconomic data were supplied by Statistics Sweden, and dates of death were retrieved from the National Death Register.

Study Cohort

We included all individuals aged ≥65 years who filled their first prescriptions for antipsychotic drugs (taken as index dates) between January 1, 2007, and December 31, 2017. All drugs belonging to group N05A of the Anatomical Therapeutic Chemical (ATC) classification system, with the exception of lithium (N05AN), were considered to be antipsychotics. A list of all antipsychotics (conventional and atypical) prescribed in the cohort is provided in Supplementary Table 1 of the Appendix. Individuals who filled prescriptions between July 1, 2005, and December 31, 2006, were excluded to ensure an exposure-free period of ≥18 months before the first possible index date. Each selected individual was matched by sex and birth year to one control individual with no antipsychotic drug prescription between July 1, 2005, and the index date. The controls were given the index date of their respective case.

Baseline and Outcome Variables

All diagnoses were coded according to the *International Classification of Diseases, Tenth Revision*. The outcome variable, hip fracture, was defined to include all events registered using code S72 in the period extending from 1 year before to 1 year after the index date. When this diagnosis was recorded more than once during a 6-month period, only the first record was used in the analyses to avoid registry of records for follow-up visits as new fractures. In addition, only main diagnoses were counted to avoid misclassification of previous fractures. Baseline data were collected at the index date and 1 year before that date. Multivariable analyses were adjusted for sex, age, highest educational level, marital status, early retirement, foreign background, in-home care, residential care, income, alcohol intoxication, diabetes, kidney failure, major NCD, malignant disease, myocardial infarction, osteoporosis, rheumatic disease, stroke, and the use of systemic glucocorticoids, anxiolytics, hypnotics, and antidepressants. The selection of variables was based on scientifically established associations, as well as the clinical experience of the authors.

Ethical Considerations

The Regional Ethical Review Board of Umeå, Sweden, and the National Board of Health and Welfare in Sweden approved this study. Both institutions waived the requirement for informed consent.

Statistical Analyses

When studying the association between the use of antipsychotics and hip fracture, Schoenfeld residuals were used to investigate time dependency, which was established. Survival analyses were performed using flexible parametric survival models for nonproportional hazards, as described by Royston and Parmar, to avoid complications that could arise in Cox regression models when allowing for time-dependent covariates.[21–23] Two independent analyses were conducted to examine retrospective and prospective hip fractures within 1 year of the index date, using the hazard scale of the stpm2 module in Stata v 13 (StataCorp, College Station, TX), with 3 degrees of freedom and all other options at default positions. The models were adjusted for sex and age but not adjusted further. Conditional logistic regression models were used to investigate the magnitude of the association between antipsychotic use and hip fracture in 10 time frames (1–15, 16–30, 31–91, 92–182, and 183–365 days before and after the initiation of therapy). Each case–control pair was excluded from further analyses if the case stopped using antipsychotics (defined at 90 days after the last prescription was filled), if the control started using antipsychotics, if either individual sustained a hip fracture or died within a time frame closer to the index date, or when December 31, 2017, was reached. Simple conditional logistic regression analyses, adjusted for sex and age through matching, as well as multivariable conditional logistic regression models were examined.[24] The latter were adjusted for conditions present at the index date in the prospective models and for all conditions present 1 year before the index date in the retrospective models.

For subgroup analyses, separate conditional logistic regression models were created for users of conventional and atypical antipsychotics, for men and women, and for individuals aged <85 and ≥85 years. For the 2 most commonly used antipsychotics, risperidone (ATC code N05AX08) and haloperidol (ATC code N05AD01), higher and lower doses were compared (≥0.5 mg vs <0.5 mg and ≥1.0 mg vs <1.0 mg, respectively). The analyses of dose effects were performed using ordinary logistic regression models. Sensitivity analyses, where the participants were matched on care level and major NCD diagnosis, respectively, were performed, as were analyses of the participants who survived the 1-year follow-up.

P values of ≤0.05 were considered to be significant and testing was 2 tailed. The statistical analyses were performed using the SPSS v 25.0 for Macintosh (IBM Corporation, Armonk, NY) and Stata v 13 for Macintosh (StataCorp, College Station, TX) software.

Results

Participant Characteristics

The matched study cohort consisted of 255,274 individuals with a mean age of 81.5 (standard deviation 8.1) years; 152,890 (59.9%) individuals were women. Baseline characteristics of the users and nonusers of antipsychotics drugs are presented in Table 1. The analyses revealed group differences in almost all variables. Those who filled prescriptions of antipsychotics had more comorbidities, more often needed residential or in-home care, and more often used other prescription drugs compared with nonusers. Atypical antipsychotics were used more commonly than were conventional antipsychotics (63.4% vs 36.6%); the 2 most frequently prescribed agents were risperidone and haloperidol, used by 45.6% and 27.5% of users, respectively. The mean duration of treatment during the 1-year follow-up was 217 (standard deviation 138) days. Significant sex differences were detected in almost all background variables; women were older and more often widowed, had lower incomes, and sustained more hip fractures than did men. Medical conditions other than major NCD were distributed unevenly between the sexes. Men were more likely

Table 1
Background Characteristics of Cases and Controls

Characteristics	Antipsychotic Drug Users, at Index Date (n = 127,637), %	Antipsychotic Drug Nonusers, at Index Date (*n* = 127,637), %	*P* Value
Age, mean (SD), y	81.5 (8.1)	81.5 (8.1)	
Highest educational level			<.001
Unspecified	2.6	3.3	
Primary school, <9 y	46.3	41.4	
Primary school, 9 y	6.4	6.9	
Secondary school, 2 y	24.1	23.6	
Secondary school, 3 y	7.3	8.4	
University, <3 y	5.7	6.7	
University, ≥3 y	7.6	9.7	
Marital status			<.001
Married	46.9	52.1	
Unmarried	8.8	6.8	
Divorced	15.4	12.4	
Widowed	29.0	28.7	
Early retirement (age <65 y)	7.0	3.6	<.001
Foreign background	11.3	11.3	.7
In-home care	28.8	20.0	<.001
Residential care	38.1	8.7	<.001
Income, mean (SD), 1000 SEK/y	138 (186)	148 (249)	<.001
Medical conditions*			
Alcohol intoxication, ever	3.0	0.8	<.001
Chronic obstructive pulmonary disease	5.2	3.1	<.001
Diabetes	16.6	12.6	<.001
Kidney failure, ever	3.6	1.9	<.001
Major NCD	30.4	4.6	<.001
Malignant disease, ever	28.9	23.8	<.001
Myocardial infarction, ever	10.2	7.9	<.001
Osteoporosis	12.4	10.4	<.001
Rheumatic disease	2.0	1.7	<.001
Stroke, ever	16.2	8.7	<.001
Drug use			
Antipsychotic drug classes†			
Conventional antipsychotics	36.6	-	
Atypical antipsychotics	63.4	-	
Individual antipsychotic drugs (ATC code)†			
Levomepromazine (N05AA02)	3.6	-	
Haloperidol (N05AD01)	27.5	-	
Olanzapine (N05AH03)	6.9	-	
Quetiapine (N05AH04)	7.2	-	
Risperidone (N05AX08)	45.6	-	
Other drugs (ATC code)‡			
Glucocorticoids, systemic (H02AB)	26.7	20.6	<.001
Anxiolytics (N05B)	60.3	24.0	<.001
Hypnotics (N05C)	63.4	35.0	<.001
Antidepressants (N06A)	57.3	22.1	<.001
Incidence of adverse events†			
Deceased within 1 year	33.0	3.9	<.001
Hip fracture the year before the index date	4.7 (*n* = 5940)	1.3 (*n* = 1723)	<.001
Hip fracture the year after the index date	3.2 (*n* = 4144)	0.9 (*n* = 1114)	<.001
Antipsychotic drug treatment duration, 1 y follow-up, mean (SD), d†,§	217 (138)	-	
Antipsychotic drug treatment duration, full follow-up, mean (SD), d†,‖	507 (670)	-	
Retrospective follow-up time, mean (SD), d	354 (53)	362 (25)	<.001
Prospective follow-up time, mean (SD), d	213 (138)	216 (138)	<.001

SD, standard deviation; SEK, Swedish krona.

*Medical conditions were registered dichotomously and included only those registered in specialized care. The presence of major NCD, diabetes, and osteoporosis was determined based on diagnoses and the use of disease-specific drugs. Stroke includes ischemic and hemorrhagic stroke.

†Not included as covariates in the multivariate analyses.

‡Designates drug use in 2005 or later.

§Investigated until December 31, 2017, but no more than 1 year after the index date.

‖Investigated until December 31, 2017.

to receive haloperidol, and women were more commonly prescribed risperidone and had longer treatment times than men (Supplementary Table 2).

Hip Fracture Incidence

In the years before and after the index date, respectively, 7663 and 5258 hip fractures were registered; 236 individuals sustained hip fractures both before and after the index date. Those who filled prescriptions of antipsychotics had a higher incidence of hip fracture than did nonusers, before (4.7% vs 1.3%) and after (3.2% vs 0.9%) the initiation of antipsychotic treatment (Table 1). The hip fracture incidence in each of the 10 time frames analyzed is presented in Supplementary Table 3, along with the numbers of participants available for analysis. The highest hip fracture incidence rates were seen in the 3 time frames preceding the index date, peaking (at 18.4/100,000 participant days) 16–30 days before the initiation of antipsychotic drug treatment. Data from 134,053 (52.5%) participants were available for analysis in the time frame with the least amount of available data, 183–365 days after the initiation of treatment (Supplementary Table 3).

Associations Between Antipsychotic Drug Use and Hip Fracture

Figure 1 shows the association between antipsychotic drug use and hip fracture, and how it changed over time. The association was present 1 year before the initiation of treatment and increased in magnitude approaching the index date, then gradually fell to plateau soon after the index date. The fully adjusted conditional logistic regression models revealed associations in all 10 studied time frames, which peaked 16–30 days before the initiation of treatment [odds ratio (OR) 9.09; 95% confidence interval (CI) 7.00–11.81; Table 2]. In the corresponding prospective time frame, 16–30 days after the index date, the OR was reduced to 3.27 (95% CI 2.36–4.51); this association strength was sustained for the remainder of the follow-up period. The pattern was similar in women and men (Table 2), in participants aged <85 and ≥85 years (Table 3), and in users of conventional and atypical antipsychotics (Table 3); all showed associations in all time frames, peaking 16–30 days before the initiation of treatment.

Dose Effects

Fully adjusted nonconditional logistic regression models revealed no dose-associated difference in the risk of hip fracture in

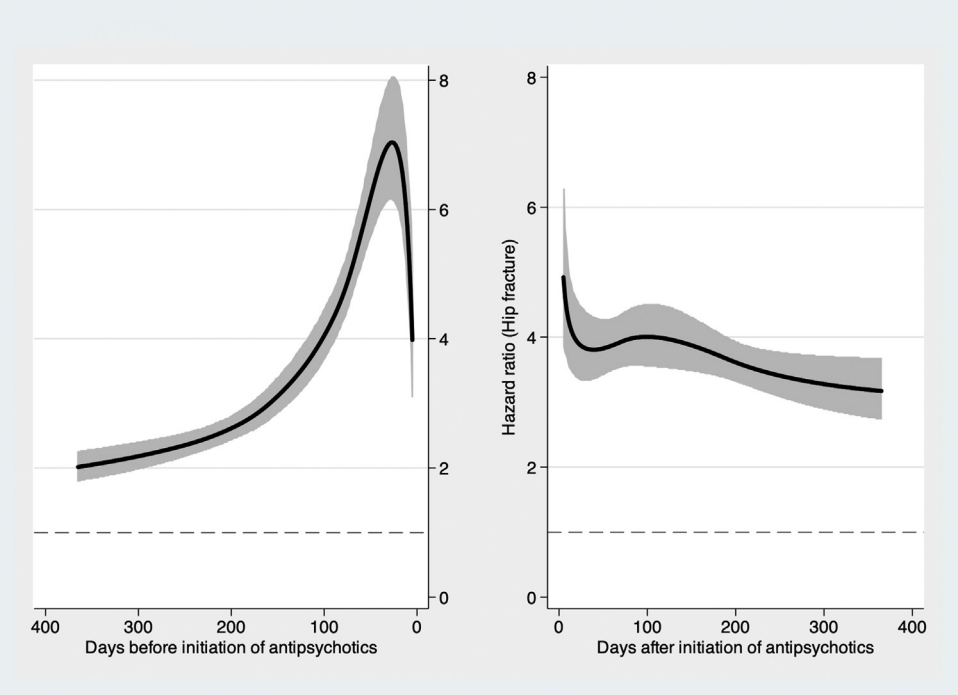

Fig. 1. Associations between antipsychotic drug treatment initiation and hip fracture. Flexible parametric models for all participants and all antipsychotics before and after treatment initiation, with antipsychotic nonusers serving as the reference. Conditional analyses were performed using 3 degrees of freedom and knots at default positions. The gray area represents the 95% CI. Each case–control pair was censored if the case stopped using antipsychotics, if the control started using antipsychotics, if either individual sustained a hip fracture or died, or when December 31, 2017, was reached.

the prospective time frames for haloperidol or risperidone users (Table 4). In the retrospective time frames, the only group difference was detected for risperidone; users who were later prescribed higher doses were less likely to sustain hip fractures at 183–365 days before the initiation of treatment than were those prescribed lower doses.

The Appendix provides the results of the simple logistic regression models, additional background data, and the results of sensitivity analyses (Supplementary Tables 1–10). Results from the analyses where the participants were matched on care level (Supplementary Table 8), on major NCD status (Supplementary Table 9), and of the subcohort of survivors (Supplementary Table 10) were similar to those of the main analyses, with the highest ORs in the time frames closely preceding the index date.

Discussion

In this nationwide Swedish matched cohort of people aged ≥65 years, a strong association was found between antipsychotic drug therapy and hip fracture. However, the association was present, and strongest, before the initiation of treatment. This pattern was independent of a rich set of potentially confounding variables and was consistent in several subgroup analyses. Finally, the risk of hip fracture

Table 2
Multivariable Conditional Logistic Regression Results for Associations Between Antipsychotic Drug Treatment Initiation and Hip Fracture

Time Frames	OR (95% CI)		
	All Participants (n = 255,274)	Women (n = 152,890)	Men (n = 102,384)
Before initiation of treatment, d			
183–365	1.75 (1.58–1.93)	1.74 (1.55–1.95)	1.72 (1.42–2.08)
92–182	3.28 (2.89–3.73)	3.05 (2.63–3.53)	4.00 (3.09–5.18)
31–91	5.63 (4.90–6.45)	4.91 (4.19–5.75)	7.81 (5.94–10.26)
16–30	9.09 (7.00–11.81)	7.83 (5.72–10.72)	12.17 (7.56–19.60)
1–15	5.84 (4.42–7.71)	4.44 (3.24–6.09)	11.70 (6.42–21.33)
After initiation of treatment, d			
1–15	4.31 (3.05–6.10)	3.58 (2.47–5.20)	9.03 (3.43–23.76)
16–30	3.27 (2.36–4.51)	2.46 (1.71–3.52)	8.45 (4.01–17.83)
31–91	3.24 (2.67–3.93)	2.74 (2.19–3.43)	4.83 (3.31–7.05)
92–182	3.30 (2.70–4.04)	2.84 (2.26–3.57)	5.33 (3.50–8.11)
183–365	2.86 (2.40–3.39)	2.38 (1.97–2.87)	5.28 (3.55–7.84)

Nonusers of antipsychotics served as the reference in all analyses. All models were adjusted for sex and age through matching. All analyses were adjusted for marital status, level of education, early retirement, foreign background, care level, and income at the index date. All prospective analyses were adjusted for alcohol intoxication, chronic obstructive pulmonary disease, diabetes, kidney failure, major NCD, malignant disease, myocardial infarction, osteoporosis, rheumatic disease, stroke, and the use of glucocorticoids, anxiolytics, hypnotics, and antidepressants at the index date. All retrospective analyses were adjusted for the same conditions at 1 year before the index date. Each case–control pair was excluded from further analyses if the case stopped using antipsychotics, if the control started using antipsychotics, if either individual sustained a hip fracture or died in a time frame closer to the index date, or when December 31, 2017, was reached.

Table 3
Multivariable Conditional Logistic Regression Results for Associations Between Antipsychotic Drug Treatment Initiation and Hip Fracture in Subgroups

Time Frames	OR (95% CI)			
	Age <85 y (n = 152,614)	Age ≥85 y (n = 102,660)	Conventional Antipsychotics (n = 93,508)	Atypical Antipsychotics (n = 161,766)
Before initiation of treatment, d				
183–365	1.90 (1.59–2.28)	1.66 (1.48–1.86)	1.54 (1.32–1.80)	1.91 (1.68–2.17)
92–182	3.70 (2.93–4.66)	2.96 (2.55–3.44)	3.08 (2.50–3.79)	3.46 (2.94–4.08)
31–91	7.37 (5.74–9.46)	4.56 (3.88–5.36)	5.44 (4.35–6.81)	5.66 (4.75–6.73)
16–30	11.01 (6.98–17.37)	7.95 (5.79–10.92)	13.89 (8.72–22.12)	7.49 (5.44–10.31)
1–15	8.14 (4.91–13.51)	4.54 (3.27–6.30)	8.28 (5.09–13.47)	4.96 (3.51–7.00)
After initiation of treatment, d				
1–15	5.76 (3.01–11.01)	3.66 (2.47–5.45)	2.22 (1.25–3.93)	6.29 (4.06–9.75)
16–30	3.72 (2.00–6.92)	2.89 (2.01–4.16)	3.42 (2.10–5.58)	3.09 (1.99–4.80)
31–91	3.90 (2.68–5.68)	2.77 (2.22–3.45)	3.03 (2.20–4.18)	3.00 (1.95–4.62)
92–182	3.80 (2.65–5.44)	2.86 (2.26–3.62)	2.78 (1.94–3.99)	3.53 (2.77–4.51)
183–365	3.62 (2.66–4.94)	2.31 (1.89–2.82)	3.83 (2.79–5.24)	2.52 (2.05–3.09)

Nonusers of antipsychotics served as the reference in all analyses. All models were adjusted for sex and age through matching. All analyses were adjusted for marital status, level of education, early retirement, foreign background, care level, and income at the index date. All prospective analyses were adjusted for alcohol intoxication, chronic obstructive pulmonary disease, diabetes, kidney failure, major NCD, malignant disease, myocardial infarction, osteoporosis, rheumatic disease, stroke, and the use of glucocorticoids, anxiolytics, hypnotics, and antidepressants at the index date. All retrospective analyses were adjusted for the same conditions at 1 year before the index date. Each case–control pair was excluded from further analyses if the case stopped using antipsychotics, if the control started using antipsychotics, if either individual sustained a hip fracture or died in a time frame closer to the index date, or when December 31, 2017, was reached.

did not differ between users of higher and lower doses of the most common antipsychotics.

Interpretation

The results of the prospective analyses performed in the present study confirm those of several previous observational studies of the association between antipsychotic drug treatment and hip fracture. The current study adds perspective, however, through analysis of the association before the initiation of treatment. Our finding that the risk of hip fracture in the treatment group was not only elevated, but highest, before the start of treatment raises questions about the causality of the relationship between the use of antipsychotics and hip fracture, as does the lack of a dose-response relationship. Compared with nonusers, antipsychotic drug users included in this study were more burdened by disease, frailty, and care dependence. Adjustment of the analyses for these variables, however, made little difference in the results, as did the strategies of more closely matching in the sensitivity analyses. This situation highlights the difficulties of handling residual confounding and, perhaps to a greater extent confounding by indication, challenges often encountered when performing observational studies. In the retrospective analyses, although no group had received antipsychotics, the risk of hip fracture was elevated among subsequent users 1 year before treatment initiation and increased gradually, peaking 16–30 days before the initiation of treatment. This pattern may represent a period of general decline in health, which increases the risks of hip fracture and the development of symptoms leading to the prescription of antipsychotics. The marked peak in the association 16–30 days before the index date could also have been amplified by hospitalisation following hip fracture, during which close monitoring by medical staff would increase the likelihood that pre-existing conditions, such as neuropsychiatric symptoms, would be detected and that treatment would be initiated. Psychotic symptoms and/or delirium could also be induced or aggravated by surgery and hospitalization, which in turn would lead to the prescription of antipsychotic drugs and filling of these prescriptions after discharge from the hospital if the psychotic or delirious state still prevailed.

The associations were similar in users of conventional and atypical antipsychotics, both peaking 16–30 days before the initiation of treatment. However, the risk seemed to decline more drastically following treatment initiation in those receiving conventional antipsychotics. This result could represent a group difference in residual hip fracture risk attributable to the treatment, but is more likely to represent confounding by indication. In support, the risk of hip fracture was not greater in individuals on higher doses of antipsychotics. Furthermore, haloperidol, by far the most commonly used conventional antipsychotic agent in this cohort, is commonly prescribed to treat terminal delirium and nausea in patients receiving palliative care, who are often bedridden and closely monitored and, thus, less likely to sustain hip fractures. Another finding of interest is the stronger association between the use of antipsychotics and hip fracture in men than in women, with nonoverlapping CIs in several time frames. Previous research has revealed sex differences in the use of

Table 4
Multivariable Unconditional Logistic Regression Results for Associations Between Antipsychotic Drug Initiation and Hip Fracture According to Dose

Time Frames	OR (95% CI)	
	Haloperidol*, N05AD01 (n = 35,133)	Risperidone†, N05AX08 (n = 58,219)
Before initiation of treatment, d		
183–365	1.08 (0.89–1.30)	0.63 (0.49–0.82)
92–182	1.18 (0.96–1.45)	0.81 (0.63–1.05)
31–91	1.18 (0.98–1.43)	0.79 (0.61–1.01)
16–30	1.30 (0.98–1.72)	1.03 (0.71–1.48)
1–15	1.06 (0.77–1.47)	1.20 (0.77–1.86)
After initiation of treatment, d		
1–15	0.94 (0.63–1.42)	0.57 (0.32–1.03)
16–30	0.82 (0.54–1.25)	1.01 (0.56–1.81)
31–91	0.97 (0.74–1.26)	0.97 (0.72–1.30)
92–182	1.10 (0.80–1.50)	1.19 (0.91–1.55)
183–365	1.04 (0.79–1.36)	0.92 (0.72–1.16)

Users of lower doses served as the reference in all analyses. All analyses were adjusted for sex, age, marital status, level of education, early retirement, foreign background, care level, and income at the index date. All prospective analyses were adjusted for alcohol intoxication, chronic obstructive pulmonary disease, diabetes, kidney failure, major NCD, malignant disease, myocardial infarction, osteoporosis, rheumatic disease, stroke, and the use of glucocorticoids, anxiolytics, hypnotics, and antidepressants at the index date. All retrospective analyses were adjusted for the same conditions at 1 year before the index date. Each individual was excluded from further analyses if she/he stopped using antipsychotics, if she/he sustained a hip fracture or died in a time frame closer to the index date, or when December 31, 2017, was reached.

*Lower dose, <1.0 mg (n = 23,563); higher dose, ≥1.0 mg (n = 11,570).

†Lower dose, <0.5 mg (n = 51,195); higher dose, ≥0.5 mg (n = 7024).

antipsychotics and in the prevalence of various neuropsychiatric symptoms among individuals with major NCD, with women found to be more likely to develop depressive symptoms and men to more often exhibit aggressive behavior.[25] One could speculate that aggression would be more likely to lead to injurious falls and to the prescription of antipsychotics.

Previous Research

Associations between antipsychotic drug treatment and hip fracture have been detected in several observational studies, many of which have been included in recent meta-analyses.[15,16] Papola et al[16] performed a meta-analysis of 24 studies of the association between antipsychotic drug exposure and hip fracture, mainly in people aged >65 years, and reported an OR of 1.57 (95% CI 1.42–1.74) but concluded that the quality of evidence was low. In a second meta-analysis, Lee et al[15] found an association between antipsychotic use and any fracture, which was stronger for conventional than for atypical antipsychotics, among older people, and for the outcome of hip fracture. In contrast to the amount of data available from observational studies, very limited data on this association derive from randomized controlled trials (RCTs). Schneider et al[8] found no increased risk of fall, fracture, or injury in individuals prescribed either of 3 studied atypical antipsychotics compared with placebo in a sample of 421 patients with Alzheimer's disease. In the same study, no increased risk of conditions likely to predispose patients to falls and fractures, such as dizziness, gait disturbance, motor disturbance, and dyskinesia, was seen in participants randomized to antipsychotic treatment.[8] A 2006 Cochrane systematic review of RCTs of atypical antipsychotics for aggression and psychosis in individuals with Alzheimer's disease did not involve the evaluation of fracture, but revealed no increased short-term risk of fall or injury caused by risperidone or olanzapine.[12] However, many RCTs are short-term and do not systematically evaluate hip fracture. In a 2006 meta-analysis of adverse effects of atypical antipsychotics for major NCD, no increased risk of falls was found.[13] The authors state that most of the included studies did not report adverse effects with an incidence below 5% or 10%. As the mean length of the 15 studies was 12 (range 6-26) weeks and the mean number of participants 341 (range 80-652),[13] hip fracture would be unlikely to reach a 5% or 10% incidence. Despite the lack of evidence of a causal relationship, influential institutions have issued warnings based on the observed associations of antipsychotic drug use with falls and fractures. In its 2017 recommendations for good drug therapy for older individuals, the National Board of Health and Welfare in Sweden included all antipsychotics in the list of drugs increasing the risk of injurious falls.[26] The latest edition of the Beers Criteria, published by the American Geriatrics Society, recommends the avoidance of antipsychotics for patients with histories of falls and/or fractures, unless no safer alternative is available, as they may cause additional falls.[27]

Study Strengths and Weaknesses

This study involved minimal selection bias, as antipsychotic drugs are available only through prescription in Sweden, and our use of no exclusion criterion should make our results generalizable to other populations of older people using antipsychotics. Treatment initiation was defined as the date of prescription filling, resulting in the exclusion of individuals who did not fill prescriptions, but the actual occurrence and exact timing of users' treatment initiation were unknown. These factors do not, however, impact the observed pre-initiation associations, which are the most novel findings of the current study. The mortality was higher in the treatment group, which could have introduced bias through competing risk of death. However, analyses where those who died within 1 year were excluded showed results similar to those of the main analyses. We expect that little loss of data on the outcome of hip fracture and many comorbidity covariates occurred, as we had access to records of all diagnoses made in specialized care. A weakness of this study, however, is the expected significant loss of data on diagnoses established mainly in primary care in Sweden, such as major NCD, diabetes, and osteoporosis. In some cases, we managed this issue by including data on disease-specific drug use. Moreover, any missed diagnoses likely influenced the associations observed before and after the initiation of antipsychotic use in a similar manner, which is supported by the similarity of the adjusted and unadjusted models. Thus, the conclusions of the present study would not likely be changed by the inclusion of more covariates, or covariates captured with better precision. Given the novel design of the present study, which led to conclusions that contrast with those of previous meta-analyses,[15,16] testing of the design and associations found before the initiation of therapy in other nationwide cohorts would be of value, as would RCTs with systematic investigation of adverse effects, sufficiently powered to analyze the risk of hip fracture.

Conclusions and Implications

This nationwide Swedish study of people aged ≥65 years revealed an association between the use of antipsychotic drugs and hip fracture. The risk of hip fracture was greatest 16–30 days before the initiation of treatment and was not influenced by the antipsychotic dose. These findings could mean that the increased risk of hip fracture is not attributable to antipsychotic treatment, but rather that this risk increases in parallel with the risk of being prescribed an antipsychotic drug. This conclusion is supported by data from RCTs and by reports of similar associations with hip fracture that peak before the initiation of therapy with antidepressants and hypnotics.

References

1. Taipale H, Koponen M, Tanskanen A, et al. High prevalence of psychotropic drug use among persons with and without Alzheimer's disease in Finnish nationwide cohort. Eur Neuropsychopharmacol 2014;24:1729–1737.
2. Carton L, Cottencin O, Lapeyre-Mestre M, et al. Off-label prescribing of antipsychotics in adults, children and elderly individuals: A systematic review of recent prescription trends. Curr Pharm Des 2015;21:3280–3297.
3. Gustafsson M, Sandman PO, Karlsson S, et al. Association between behavioral and psychological symptoms and psychotropic drug use among old people with cognitive impairment living in geriatric care settings. Int Psychogeriatr 2013;25:1415–1423.
4. Koponen M, Tolppanen AM, Taipale H, et al. Incidence of antipsychotic use in relation to diagnosis of Alzheimer's disease among community-dwelling persons. Br J Psychiatry 2015;207:444–449.
5. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ 2015;350:h369.
6. Phan SV, Osae S, Morgan JC, et al. Neuropsychiatric Symptoms in Dementia: Considerations for Pharmacotherapy in the USA. Drugs RD 2019;19:93–115.
7. Press D. Management of neuropsychiatric symptoms of dementia. 2018. Available at: http://www.uptodate.com/contents/management-of-neuropsychiatric-symptoms-of-dementia. Accessed November 4, 2019.
8. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525–1538.
9. Schneider-Thoma J, Efthimiou O, Bighelli I, et al. Second-generation antipsychotic drugs and short-term somatic serious adverse events: A systematic review and meta-analysis. Lancet Psychiatry 2019;6:P753–P765.
10. Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. Cochrane Database Syst Rev 2002;2:CD002852.
11. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943.
12. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD003476.
13. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: Meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 2006;14:191–210.
14. Bentler SE, Liu L, Obrizan M, et al. The aftermath of hip fracture: Discharge placement, functional status change, and mortality. Am J Epidemiol 2009;170:1290–1299.

15. Lee SH, Hsu WT, Lai CC, et al. Use of antipsychotics increases the risk of fracture: A systematic review and meta-analysis. Osteopor Int 2017;28:1167–1178.
16. Papola D, Ostuzzi G, Thabane L, et al. Antipsychotic drug exposure and risk of fracture: A systematic review and meta-analysis of observational studies. Int Clin Psychopharmacol 2018;33:181–196.
17. Brannstrom J, Lovheim H, Gustafson Y, Nordstrom P. Association between antidepressant drug use and hip fracture in older people before and after treatment initiation. JAMA Psychiatry 2019;76:172–179.
18. Nordstrom P, Nordstrom A. Use of short-acting and long-acting hypnotics and the risk of fracture: A critical analysis of associations in a nationwide cohort. Osteopor Int 2019;30:1983–1993.
19. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register-Opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Safety 2007;16:726–735.
20. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
21. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002;21:2175–2197.
22. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. Annu Rev Public Health 1999;20:145–157.
23. Royston P, Lambert PC. Flexible parametric survival analysis using Stata: Beyond the Cox model. StataCorp LP; 2011.
24. Preisser JS, Koch GG. Categorical data analysis in public health. Annu Rev Public Health 1997;18:51–82.
25. Lovheim H, Sandman PO, Karlsson S, Gustafson Y. Sex differences in the prevalence of behavioral and psychological symptoms of dementia. Int Psychogeriatr 2009;21:469–475.
26. Sweden's National Board of Health and Welfare. Indicators of good drug therapy in the elderly. In: Fastbom J, ed. Indikatorer för god läkemedelsterapi hos äldre. Vol 2017-6-72017. Available at: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/ovrigt/2017-6-7.pdf. Accessed November 4, 2019.
27. Radcliff S, Yue JR, Rocco G, et al. American Geriatrics Society 2015 Updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227–2246.

Supplementary Table 1
Prescribed and Dispensed Antipsychotic Drugs in the Studied Cohort

Agents	ATC-Code	n
Conventional antipsychotics		
Chlorpromazine	N05AA01	14
Levomepromazine	N05AA02	4609
Dixyrazine	N05AB01	283
Fluphenazine	N05AB02	8
Perphenazine	N05AB03	547
Prochlorperazine	N05AB04	2662
Periciazine	N05AC01	3
Thioridazine	N05AC02	1
Haloperidol	N05AD01	35,133
Droperidol	N05AD08	76
Flupentixol	N05AF01	1519
Chlorprothixene	N05AF03	234
Zuclopenthixol	N05AF05	1659
Pimozide	N05AG02	6
Atypical antipsychotics		
Melperone	N05AD03	3067
Sertindole	N05AE03	1
Ziprasidone	N05AE04	40
Lurasidone	N05AE05	3
Clozapine	N05AH02	523
Olanzapine	N05AH03	8791
Quetiapine	N05AH04	9214
Sulpiride	N05AL01	2
Amisulpride	N05AL05	1
Risperidone	N05AX08	58,219
Aripiprazole	N05AX12	973
Paliperidone	N05AX13	49

Supplementary Table 2
Background Characteristics of Women and Men

Characteristics	Women, at Index Date (n = 152,890), %	Men, at Index Date (n = 102,384), %	*P* Value
Age, mean (SD), y	82.5 (8.1)	80.1 (7.8)	<.001
Highest educational level			<.001
Unspecified	3.5	2.2	
Primary school, <9 y	45.1	41.9	
Primary school, 9 y	7.9	4.8	
Secondary school, 2 y	26.5	19.8	
Secondary school, 3 y	3.9	13.9	
University, <3 y	5.8	6.7	
University, ≥3 y	7.2	10.8	
Marital status			<.001
Married	39.2	64.8	
Unmarried	6.5	9.8	
Divorced	14.3	13.4	
Widowed	40.0	12.0	
Early retirement (age <65 y)	5.3	5.4	.5
Foreign background	11.9	10.5	<.001
In-home care	27.0	20.4	<.001
Residential care	26.2	19.3	<.001
Income, mean (SD), 1000 SEK/y	123 (126)	174 (309)	<.001
Medical conditions*			
Alcohol intoxication, ever	0.9	3.3	<.001
Chronic obstructive pulmonary disease	3.8	4.7	<.001
Diabetes	12.8	17.4	<.001
Kidney failure, ever	1.9	3.9	<.001
Major NCD	17.4	17.6	.2
Malignant disease, ever	24.9	28.5	<.001
Myocardial infarction, ever	7.1	12.1	<.001
Osteoporosis	16.5	3.7	<.001
Rheumatic disease	2.2	1.3	<.001
Stroke, ever	11.0	14.6	<.001
Drug use			
Antipsychotic drug classes†			
Conventional antipsychotics	17.7	19.2	<.001
Atypical antipsychotics	32.3	30.8	<.001
Individual antipsychotic drugs (ATC code)†			
Levomepromazine (N05AA02)	1.6	2.1	<.001
Haloperidol (N05AD01)	13.1	14.7	<.001
Olanzapine (N05AH03)	3.5	3.4	.5
Quetiapine (N05AH04)	3.1	4.3	<.001
Risperidone (N05AX08)	23.9	21.1	<.001
Other drugs (ATC code)‡			
Glucocorticoids, systemic (H02AB)	24.4	22.6	<.001
Anxiolytics (N05B)	46.2	36.1	<.001
Hypnotics (N05C)	52.8	43.9	<.001
Antidepressants (N06A)	43.9	33.4	<.001
Incidence of adverse events†			
Deceased within 1 y	16.7	21.1	<.001
Hip fracture the year before the index date	3.5 (n = 5369)	2.2 (n = 2294)	<.001
Hip fracture the year after the index date	2.4 (n = 3725)	1.5 (n = 1533)	<.001
Antipsychotic drug treatment duration, 1 y follow-up, mean (SD), d†,§	226 (136)	203 (139)	<.001
Antipsychotic drug treatment duration, full follow-up, mean (SD), d†,‖	547 (697)	448 (622)	<.001
Retrospective follow-up time, mean (SD), d	357 (45)	360 (38)	<.001
Prospective follow-up time, mean (SD), d	223 (137)	202 (139)	<.001

SD, standard deviation; SEK, Swedish krona.

*Medical conditions were registered dichotomously and included only those registered in specialized care. The presence of major NCD, diabetes, and osteoporosis was determined based on diagnoses and the use of disease-specific drugs. Stroke includes ischemic and hemorrhagic stroke.

†Not included as covariates in the multivariate analyses.

‡Designates drug use in 2005 or later.

§Investigated until December 31, 2017, but no more than 1 year after the index date.

‖Investigated until December 31, 2017.

Supplementary Table 3
Hip Fracture Incidence and Data Available for Analysis

Time Frames	N		
	Available for Analysis*	Hip Fractures†	Hip Fractures per 100,000 Participant Days
Before initiation of treatment, d			
183–365	250,283	2672	5.8
92–182	252,127	1844	8.0
31–91	254,075	1948	12.6
16–30	254,778	703	18.4
1–15	255,274	496	13.0
After initiation of treatment, d			
1–15	255,274	444	11.6
16–30	239,196	398	11.1
31–91	229,701	1305	9.3
92–182	167,521	1279	8.4
183–365	134,053	1832	7.5

*Each case–control pair was excluded from further analyses if the case stopped using antipsychotics (defined at 90 days after the last prescription was filled), if the control started using antipsychotics, if either individual sustained a hip fracture or died in a time frame closer to the index date, or when December 31, 2017, was reached.

†Crude numbers for all participants.

Supplementary Table 4
Background Characteristics at Index Date and 1 Year Before

Characteristics	All Participants, at Index Date (n = 255,274), %	All Participants, 1 y before (n = 255,274), %
Age, mean (SD), y	81.5 (8.1)	80.5 (8.1)
Highest educational level		*
Unspecified	3.0	
Primary school, <9 y	43.8	
Primary school, 9 y	6.7	
Secondary school, 2 y	23.8	
Secondary school, 3 y	7.9	
University, <3 y	6.2	
University, ≥3 y	8.6	
Marital status		*
Married	49.5	
Unmarried	7.8	
Divorced	13.9	
Widowed	28.8	
Early retirement (age <65 y)	5.3	*
Foreign background	11.3	*
In-home care	24.4	20.2
Residential care	23.4	11.5
Income, mean (SD), 1000 SEK/y	143 (220)	*
Medical conditions†		
Alcohol intoxication, ever	1.9	1.6
Chronic obstructive pulmonary disease	4.2	3.5
Diabetes	14.6	13.9
Kidney failure, ever	2.7	1.9
Major NCD	17.5	11.5
Malignant disease, ever	26.3	23.6
Myocardial infarction, ever	9.1	8.0
Osteoporosis	11.4	10.1
Rheumatic disease	1.9	1.8
Stroke, ever	12.4	10.0
Drug use		
Antipsychotic drug classes‡		
Conventional antipsychotics	18.3	-
Atypical antipsychotics	31.7	-
Individual antipsychotic drugs (ATC code)‡		
Levomepromazine (N05AA02)	1.8	-
Haloperidol (N05AD01)	13.8	-
Olanzapine (N05AH03)	3.4	-
Quetiapine (N05AH04)	3.6	-
Risperidone (N05AX08)	22.8	-
Other drugs (ATC code)§		
Glucocorticoids, systemic (H02AB)	23.7	19.2
Anxiolytics (N05B)	42.2	29.5
Hypnotics (N05C)	49.2	38.8
Antidepressants (N06A)	39.7	30.7
Incidence of adverse events‡		
Deceased within 1 y	18.4	-
Hip fracture the year before the index date	3.0 (n = 7663)	-
Hip fracture the year after the index date	2.1 (n = 5258)	-
Retrospective follow-up time, mean (SD), d	358 (42)	-
Prospective follow-up time, mean (SD), d	215 (138)	-

SD, standard deviation; SEK, Swedish krona.

*Investigated only at the index date.

†Medical conditions were registered dichotomously and included only those registered in specialized care. The presence of major NCD, diabetes, and osteoporosis was determined based on diagnoses and the use of disease-specific drugs. Stroke includes ischemic and hemorrhagic stroke.

‡Not included as covariates in the multivariate analyses.

§Designates drug use in 2005 or later.

Supplementary Table 5
Simple Conditional Logistic Regression Results for Associations Between Antipsychotic Drug Treatment Initiation and Hip Fracture

Time Frames	OR (95% CI)		
	All Participants (n = 255,274)	Women (n = 152,890)	Men (n = 102,384)
Before initiation of treatment, d			
183–365	2.33 (2.14–2.53)	2.25 (2.04–2.49)	2.53 (2.15–2.98)
92–182	3.52 (3.15–3.93)	3.28 (2.89–3.73)	4.27 (3.42–5.33)
31–91	5.21 (4.61–5.88)	4.59 (3.98–5.28)	7.19 (5.64–9.17)
16–30	8.09 (6.39–10.25)	7.11 (5.35–9.46)	10.39 (6.77–15.94)
1–15	5.65 (4.41–7.23)	4.39 (3.31–5.82)	10.60 (6.24–18.00)
After initiation of treatment, d			
1–15	5.17 (4.10–6.65)	3.98 (3.02–5.25)	13.44 (6.83–26.46)
16–30	3.85 (3.02–4.91)	2.96 (2.25–3.88)	8.62 (4.85–15.30)
31–91	3.80 (3.32–4.34)	3.37 (2.88–3.95)	5.01 (3.88–6.48)
92–182	4.00 (3.49–4.60)	3.75 (3.20–4.39)	4.85 (3.66–6.42)
183–365	3.48 (3.11–3.89)	2.87 (2.53–3.25)	6.48 (5.01–8.38)

Nonusers of antipsychotics served as the reference in all analyses. All models were adjusted for sex and age through matching. Each case–control pair was excluded from further analyses if the case stopped using antipsychotics, if the control started using antipsychotics, if either individual sustained a hip fracture or died in a time frame closer to the index date, or when December 31, 2017, was reached.

Supplementary Table 6
Simple Conditional Logistic Regression Results for Associations Between Antipsychotic Drug Treatment Initiation and Hip Fracture in Subgroups

Time Frames	OR (95% CI)			
	Age <85 y (n = 152,614)	Age ≥85 y (n = 102,660)	Conventional Antipsychotics (n = 93,508)	Atypical Antipsychotics (n = 161,766)
Before initiation of treatment, d				
183–365	2.96 (2.57–3.42)	2.03 (1.82–2.25)	2.04 (1.78–2.35)	2.50 (2.25–2.78)
92–182	4.52 (3.73–5.47)	3.06 (2.67–3.50)	3.27 (2.72–3.93)	3.67 (3.19–4.21)
31–91	7.67 (6.18–9.52)	4.15 (3.58–4.82)	5.64 (4.60–6.92)	4.98 (4.28–5.79)
16–30	9.68 (6.56–14.28)	7.18 (5.33–9.69)	11.55 (7.47–17.85)	6.71 (5.05–8.91)
1–15	8.52 (5.53–13.13)	4.35 (3.21–5.90)	8.33 (5.30–13.10)	4.59 (3.41–6.17)
After initiation of treatment, d				
1–15	6.75 (4.38–10.36)	4.38 (3.20–5.99)	4.41 (2.90–6.69)	5.62 (4.09–7.72)
16–30	6.76 (4.28–10.69)	2.85 (2.13–3.82)	4.53 (3.09–6.65)	3.42 (2.50–4.69)
31–91	5.73 (4.55–7.21)	2.91 (2.46–3.44)	3.63 (2.89–4.57)	3.88 (3.29–4.58)
92–182	5.54 (4.42–6.94)	3.17 (2.65–3.78)	2.88 (3.01–5.00)	4.06 (3.44–4.78)
183–365	5.39 (4.49–6.47)	2.48 (2.15–2.86)	4.22 (3.38–5.27)	3.24 (2.85–3.68)

Nonusers of antipsychotics served as the reference in all analyses. All models were adjusted for sex and age through matching. Each case–control pair was excluded from further analyses if the case stopped using antipsychotics, if the control started using antipsychotics, if either individual sustained a hip fracture or died in a time frame closer to the index date, or when December 31, 2017, was reached.

Supplementary Table 7
Simple Unconditional Logistic Regression Results for Associations Between Antipsychotic Drug Initiation and Hip Fracture According to Dose

Time Frames	OR (95% CI)	
	Haloperidol*, N05AD01 (n = 35,133)	Risperidone†, N05AX08 (n = 58,219)
Before initiation of treatment, d		
183–365	1.17 (0.97–1.41)	0.59 (0.46–0.77)
92–182	1.18 (0.96–1.45)	0.82 (0.63–1.06)
31–91	1.17 (0.98–1.41)	0.85 (0.66–1.08)
16–30	1.23 (0.93–1.63)	1.13 (0.78–1.62)
1–15	1.07 (0.78–1.47)	1.25 (0.81–1.94)
After initiation of treatment, d		
1–15	1.01 (0.67–1.52)	0.57 (0.32–1.03)
16–30	0.79 (0.52–1.19)	1.03 (0.58–1.84)
31–91	1.05 (0.81–1.36)	0.92 (0.68–1.23)
92–182	1.20 (0.88–1.63)	1.17 (0.90–1.52)
183–365	1.04 (0.80–1.36)	0.90 (0.71–1.14)

Users of lower doses served as the reference in all analyses. All analyses were adjusted for sex and age. Each individual was excluded from further analyses if she/he stopped using antipsychotics, if she/he sustained a hip fracture or died in a time frame closer to the index date, or when December 31, 2017, was reached.

*Lower dose, <1.0 mg (n = 23,563); higher dose, ≥1.0 mg (n = 11,570).

†Lower dose, <0.5 mg (n = 51,195); higher dose, ≥0.5 mg (n = 7024).

Supplementary Table 8
Simple Conditional Logistic Regression Results for Associations Between Antipsychotic Drug Treatment Initiation and Hip Fracture in Subgroups Based on Care Level

Time Frames	OR (95% CI)		
	No Care (n = 71,980)	In-Home Care (n = 16,286)	Residential Care (n = 12,202)
Before initiation of treatment, d			
183–365	2.96 (2.57–3.42)	0.95 (0.71–1.26)	1.08 (0.86–1.35)
92–182	4.52 (3.73–5.47)	1.42 (1.03–1.96)	1.95 (1.43–2.66)
31–91	9.61 (6.25–9.52)	2.67 (1.93–3.68)	2.40 (1.73–3.34)
16–30	14.57 (6.78–31.34)	5.08 (2.80–9.20)	4.25 (1.97–9.18)
1–15	28.33 (8.96–89.60)	2.46 (1.29–4.69)	3.13 (1.41–6.93)
After initiation of treatment, d			
1–15	13.00 (4.70–35.93)	4.63 (2.15–9.93)	1.67 (0.82–3.41)
16–30	13.60 (5.48–33.72)	2.50 (1.28–4.88)	2.00 (0.97–4.12)
31–91	4.34 (2.96–6.38)	2.70 (1.74–4.20)	1.54 (1.03–2.30)
92–182	4.97 (3.40–7.26)	2.67 (1.67–4.26)	1.94 (1.26–2.99)
183–365	5.14 (3.71–7.13)	2.06 (1.49–2.84)	1.89 (1.26–2.83)

Nonusers of antipsychotics served as the reference in all analyses. All models were adjusted for sex, age and care level through matching. Each case–control pair was excluded from further analyses if the case stopped using antipsychotics, if the control started using antipsychotics, if either individual sustained a hip fracture or died in a time frame closer to the index date, or when December 31, 2017, was reached.

Supplementary Table 9
Simple Conditional Logistic Regression Results for Associations Between Antipsychotic Drug Treatment Initiation and Hip Fracture in Subgroups Based on Major NCD Status

Time Frames	OR (95% CI)	
	Major NCD (n = 3794)	No Major NCD (n = 169,640)
Before initiation of treatment, d		
183–365	1.06 (0.67–1.67)	2.29 (2.05–2.54)
92–182	1.88 (1.02–3.44)	3.47 (3.01–4.00)
31–91	2.67 (1.24–5.74)	5.24 (4.50–6.10)
16–30	9.00 (1.14–71.04)	8.78 (6.55–11.76)
1–15	7.00 (0.86–56.89)	5.18 (3.83–7.01)
After initiation of treatment, d		
1–15	6.00 (0.72–49.84)	5.11 (3.73–7.01)
16–30	4.00 (0.45–35.79)	4.27 (3.13–5.82)
31–91	6.00 (2.33–15.46)	3.03 (2.56–3.58)
92–182	1.73 (0.82–3.63)	3.66 (3.06–4.38)
183–365	2.13 (1.16–3.94)	3.32 (2.87–3.83)

Nonusers of antipsychotics served as the reference in all analyses. All models were adjusted for sex, age, and diagnosis of major NCD through matching. Each case–control pair was excluded from further analyses if the case stopped using antipsychotics, if the control started using antipsychotics, if either individual sustained a hip fracture or died in a time frame closer to the index date, or when December 31, 2017, was reached.

Supplementary Table 10
Conditional Logistic Regression Results for Associations Between Antipsychotic Drug Treatment Initiation and Hip Fracture in 1-Year survivors

Time Frames	OR (95% CI)	
	Simple Model (n = 167,704)	Multivariable (n = 167,704)
Before initiation of treatment, d		
183–365	2.42 (2.17–2.70)	1.80 (1.58–2.05)
92–182	3.65 (3.16–4.21)	3.40 (2.87–4.04)
31–91	5.07 (4.31–5.95)	5.49 (4.56–6.60)
16–30	8.74 (6.28–12.18)	9.54 (6.60–13.78)
1–15	5.30 (3.83–7.35)	5.78 (3.97–8.42)
After initiation of treatment, d		
1–15	4.80 (3.41–6.75)	3.91 (2.37–6.47)
16–30	3.16 (2.30–4.33)	2.77 (1.76–4.38)
31–91	3.16 (2.66–3.75)	2.11 (1.62–2.74)
92–182	3.58 (3.04–4.22)	3.09 (2.42–3.96)
183–365	3.01 (2.67–3.40)	2.24 (1.85–2.71)

Nonusers of antipsychotics served as the reference in all analyses. All analyses included only the case–control pairs where both individuals were alive 1 year after the index date. All models were adjusted for sex and age through matching. All multivariable analyses were adjusted for marital status, level of education, early retirement, foreign background, care level, and income at the index date. All prospective analyses were adjusted for alcohol intoxication, chronic obstructive pulmonary disease, diabetes, kidney failure, major NCD, malignant disease, myocardial infarction, osteoporosis, rheumatic disease, stroke, and the use of glucocorticoids, anxiolytics, hypnotics, and antidepressants at the index date. All retrospective analyses were adjusted for the same conditions at 1 year before the index date. Each case–control pair was excluded from further analyses if the case stopped using antipsychotics, if the control started using antipsychotics, or if either individual sustained a hip fracture in a time frame closer to the index date, or when December 31, 2017, was reached.