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Is anticholinergic and sedative drug burden associated with postdischarge institutionalization in community-dwelling older patients acutely admitted to hospital? A Norwegian registry-based study

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Abstract

Purpose: Investigate the association between anticholinergic (AC) and sedative (SED) drug burden before hospitalization and postdischarge institutionalization (PDI) in community-dwelling older patients acutely admitted to hospital.

Methods: A cross-sectional study using data from the Norwegian Patient Registry and the Norwegian Prescription Database. We studied acutely hospitalized community-dwelling patients ≥70 years during 2013 ($N = 86\,509$). Patients acutely admitted to geriatric wards underwent subgroup analyses ($n = 1715$). We calculated drug burden by the Drug Burden Index (DBI), use of AC/SED drugs, and the number of AC/SED drugs. Piecewise linearity of DBI versus PDI and a knot point (DBI = 2.45) was identified. Statistical analyses included an adjusted multivariable logistic regression model.

Results: In the total population, 45.4% were exposed to at least one AC/SED drug, compared to 52.5% in the geriatric subgroup. AC/SED drugs were significantly associated with PDI. The DBI with odds ratios (ORs) of 1.11 (95% CI 1.07–1.15) for DBI < 2.45 and 1.08 (95% CI 1.04–1.13) for DBI ≥ 2.45. The number of AC/SED drugs with OR of 1.07 (95% CI 1.05–1.09). The AC component of DBI with OR 1.23 and the number of AC drugs with OR 1.13. In the subgroup, ORs were closer to 1 for AC drugs.

Conclusions: The use of AC/SED drugs was highly prevalent in older patients before acute hospital admissions, and significantly associated with PDI. The number, or just using AC/SED drugs, gave similar associations with PDI compared to applying the DBI. Using AC drugs showed higher sensitivity, indicating that to reduce the risk of PDI, a clinical approach could be to reduce the number of AC drugs.

KEYWORDS
anticholinergics, drug burden index, hospitalization, institutionalization, National Health Registries, older patients, sedatives

Key Points

- The use of AC/SED drugs was highly prevalent in older patients before acute hospital admissions
- We found significant relationships between AC/SED drug burden and post-discharge institutionalization, independent of whether we applied DBI scores, the dichotomous variable "using AC/SED drug(s) or not", or the number of AC/SED drugs used, both combined and separately.
- Number of AC drugs had the strongest association with PDI and reducing exposure to AC drugs can potentially reduce the risk of PDI in older hospitalized patients.
- The odds ratios for AC drugs and PDI were closer to one for the subgroup of patients admitted to a geriatric hospital ward, although not statistically significant.
- The Drug Burden Index method is complex. Several steps must be completed before DBI calculation can be executed, and the DBI scores can be challenging to use.

Plain Language Summary

Anticholinergic (AC) and sedative (SED) drugs are considered high-risk drugs for older patients. This study investigated if the use of anticholinergic (AC) and sedative (SED) drugs before hospitalization increased the risk of institutionalization (PDI) for older patients when they are discharged from hospital. We used data from the Norwegian Patient Registry and the Norwegian Prescription Database to study acutely hospitalized community-dwelling patients ≥70 years during 2013. Patients acutely admitted to geriatric wards (=geriatric group) underwent additional analyses. We measured the patients AC/SED drug burden by (i) the Drug Burden Index, (ii) whether they used AC/SED drugs (yes or no), and (iii) the number of AC/SED drugs in use. We found that 45.4% and 52.5% of the patients used one or more AC/SED drug in the total population and in the geriatric group, respectively. AC/SED drug use increased the risk of PDI in the population for all measurements. Number of AC drugs in use showed the highest risk of PDI in the full population, but not in the geriatric group. Our findings indicate that to reduce the risk of PDI in older patients, one approach could be to reduce the number of AC drugs in use.

1 | INTRODUCTION

Older people generally prefer to live at home to maintain autonomy.[1,2] However, age-related factors like frailty, falls, and cognitive impairment increases the risk of institutionalization such as admission to nursing homes.[3–7]

After acute hospitalizations, older people are commonly institutionalized, permanently, or temporarily.[8] Risk factors for acute hospital admissions are age and frailty,[9] while predictors for the transition to institutions remain uncertain.[8] Norway has a "de-institutionalization" policy to manage the aging population,[10] an unparalleled extended use of home care services to allow older people to remain home-dwelling longer before institutionalization. This policy is cost-effective and has reduced the proportion of older adults living in nursing homes .[11,12] Therefore, identifying risk factors preventing institutionalization after acute hospitalization is important to target interventions that may enable older people to remain home-dwelling.

Inappropriate drug use in older people is common[13] and known to cause serious harm.[14] The use of anticholinergic (AC) and/or sedative (SED) drugs is associated with acute and unpredictable adverse effects to which older patients are particularly susceptible.[14] Having this in mind, developing tools that could guide prescribers and health care personnel to take appropriate actions and reduce drug burden is highly relevant. Interestingly, common AC/SED effects such as agitation, cognitive impairment, and dementia-like symptoms[14] coincide with risk factors for institutionalization in older people, thus posing a potential for intervention and improvement.

The Drug Burden Index (DBI) measures the cumulative AC and SED drug burden.[15,16] DBI differs from other methods to measure drug burden in older people by including dose to adjust the score, while not considering affinity of the included drugs. Furthermore, DBI includes SED and AC drugs, whereas independently addressing AC drugs is more common.[17,18]

The DBI is widely used to assess AC/SED-burden in database studies[17] and is associated with adverse health outcomes and

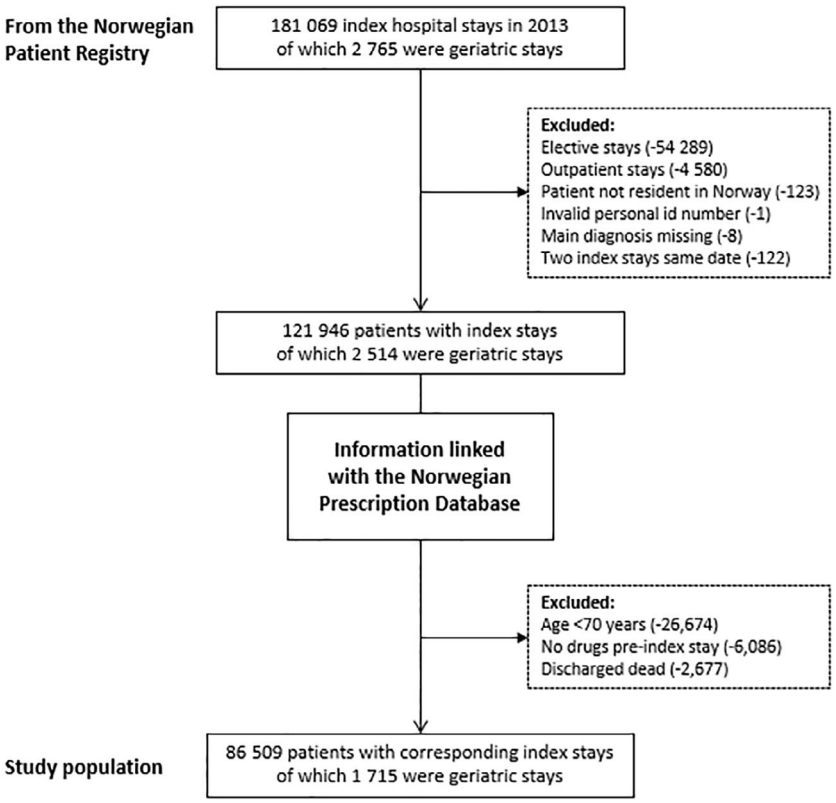

FIGURE 1 Flowchart describing the inclusion process and data merging for the study population

functional decline in older people.[15,19–25] In general, associations between drug therapy and post discharge institutionalization (PDI) have rarely been investigated,[8] while the association between DBI and PDI has not been examined.

In this study, we investigate the association between AC/SED drug burden and PDI following an acute hospital stay among community-dwelling older people and for a subgroup of patients acutely admitted to geriatric wards, that is, specialized aged care hospital wards, in Norway.

2 | METHOD

2.1 | Study design and data source

For this cross-sectional population-based study, we used data from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). NPR contains complete data on hospitalized patients,[26] while NorPD contains complete information on prescription drugs dispensed from Norwegian pharmacies to community-dwelling persons except nursing-home residents.[27] Linking of registries is possible by applying the unique personal identification number assigned all Norwegian citizens. NorPD classify drugs based on the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system[28] and includes: strength/concentration, amount, unit, administration form, and defined daily doses (DDD) dispensed.[29] For each patient we had access to data from both registries 1 year before and 1 year after the date of first hospital stay in 2013.

2.2 | Study population

The study population, see Figure 1, comprised community-dwelling persons ≥70 years with at least one admission to a somatic hospital. From NPR, we defined the first hospital stay in 2013 as the index stay (IS), except for patients with stay(s) at geriatric wards where we defined the IS as the first geriatric stay. We excluded patients with elective ISs, with >1 IS on the same date, outpatient stays, and those without a principal discharge diagnosis.

We classified and included patients as community-dwelling, hence living outside of institutions such as nursing homes, if they had at least one dispensed prescription drug identified in NorPD during 120 days before admittance, see Figure 1. We used the discharge status from NPR to identify whether a patient was discharged to an institution (including rehabilitation and nursing homes) or to *other*. The *other* category included patients who died during the hospital stay or were discharged home. Patients in the *other* category were defined as dead during the hospital stay and excluded if they met the following criteria: registered as dead between IS and date of data extract, with no hospital admission (NPR) and no medication dispensing (NorPD) after the IS's day of discharge.

2.3 | AC/SED-drug exposure at hospital admission

We defined drugs ($n = 135$) with anticholinergic and sedative properties, see Supplementary material S1. Drugs with AC properties were defined by searching in The Norwegian Pharmaceutical Product

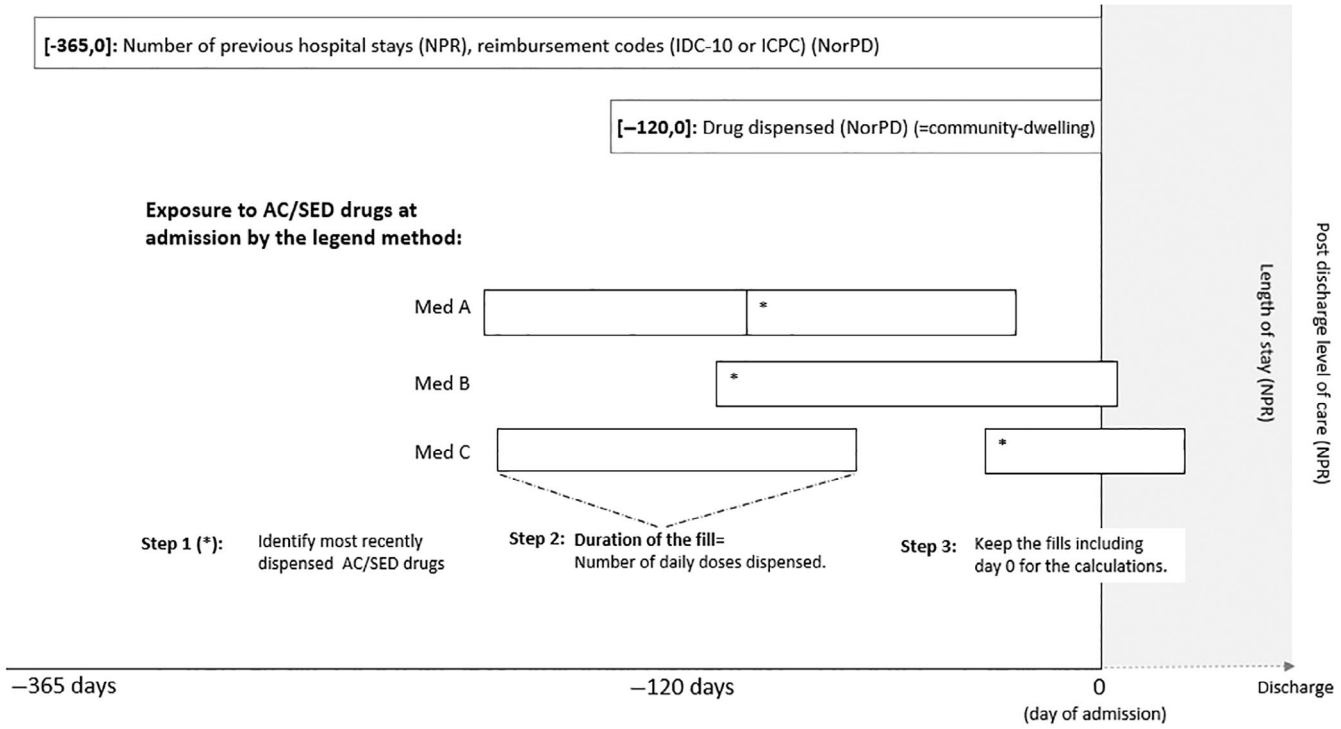

FIGURE 2 Data sources and method used to determine AC/SED drug exposure, length of index stay and postdischarge level of care. Data was collected 1 year before and after hospital admission (day 0). Top: Assessment of previous hospital stays and reimbursement codes 1 year prior to hospitalization. Status as community-dwelling was determined by using NorPD data 120 days prior to hospitalization. Bottom: Exposure to AC/SED-drugs at admission using the legend method[32] followed a three-step process: (1) We identified the most recent (re)fills for each drug defined as AC or SED, (2) Duration of the fill was estimated through the number of daily doses dispensed, that is, daily dose (*D*) = dispensed unit strength of drug*number of daily administrations, except for drugs with DDD (=defined daily doses[29]) as only information, then duration of the fill = number of DDDs dispensed, and (3) If the most recent fill lasted through day 0, it was defined as in use and included in the calculations. Hence Drug A will not be included in the DBI, while drugs B and C will. The dotted arrow between day of admission (0) and discharge indicates length of index hospital stay (shaded area). AC, Anticholinergic; SED, sedative.

Compendium (NPPC),[30] while drugs with SED properties were defined using the ATC-groups for "primary sedative" and "sedation as a prominent side effect" drugs as described by Linjakumpu et al.[31]

We identified exposure to AC/SED drugs at hospital admission by identifying the most recent pharmacy fill for each drug and applying the legend duration approach.[32,33] A drug was defined as "in use" if the dispensing lasted to the day of admission. Drug exposure assessment is displayed in Figure 2.

2.4 | Drug burden index calculation

The DBI measures cumulative exposure to AC/SED drugs through dose–response-based calculations using the DBI expression[15]:

$$\mathrm{DBI} = \sum \frac{D}{D+\delta}$$

This is a hyperbolic function where each AC/SED drug contributes to the DBI-score with a value between 0 and 1, calculated by daily dose (D) adjusted by the minimum recommended daily dose (δ). For example, a prescribed daily dose of $1 \times \delta$ will contribute to the DBI-score with a value of 0.5, while increasing the dose to a daily dose of $2 \times \delta$ increases the DBI to 0.67. Two separate drugs in minimum dose results in a DBI-score of 1. Hence, increasing the dose by one δ contributes to the DBI-score less than adding a DBI-drug in one δ.

Daily doses (*D*) in use were estimated in step 2 of the legend approach, see Figure 2. We calculated the DBI-score using the minimum recommended maintenance dose collected from the NPPC applying the following criteria: (i) the defined adult dose (or for older adults if specified), (ii) for drugs with multiple indications, the lowest minimum dose, (iii) for combination drugs, minimum dose for the AC/SED component, (iv) for drugs with different administration routes, minimum dose for each administration route, (v) if two administration routes with same ATC-code were dispensed the same day, doses were converted to equivalents in the DBI-calculations, and (vi) for drugs without listing in NPPC, i.e., without Norwegian marketing approval, the minimum dose was set to one DDD.

2.5 | Outcome

The outcome variable, postdischarge institutionalization (PDI), describes whether patients were discharged from the hospital to an institution or not.

2.6 | Covariates and factors

The number of hospital stays previous year, main ICD-10 diagnosis for the hospital stay and length of index stay were collected from NPR. Comorbidity was addressed using reimbursement codes, that is, ICD-10 or ICPC-2 from the NorPD by applying the Deyo adaption of the Charlson Comorbidity Index (CCI).[34] We also constructed a *mental illness-variable* by using reimbursement codes defining mental disorders which the CCI did not cover. From NorPD, we collected information on age and number of drugs dispensed to each patient 120 days before admission.

2.7 | Statistical analysis and modelling

Data management, descriptive analysis and DBI calculations were performed in SPSS (version 26), while the regression model was designed and analyzed in STATA MP16.0. Descriptive statistics are presented as means with standard deviations (SD) or frequencies with proportions (%). We applied Student's *t* test to compare means (continuous data; age, Charlson Comorbidity Index, previous hospital stays, number of drugs used, length of hospital stays and DBI mean score). We considered *p*-values < 0.05 statistically significant.

The linearity of DBI with the outcome variable was investigated in a weighted scatterplot to identify piecewise linearity, and where the linear pieces met, that is, corresponding knot points. Subsequently, we used the DBI in the regression model as a splined variable.[35] Splining the DBI provide opportunity to include slope changes without categorizing the variable.

The association between AC/SED exposure were investigated by (1) DBI at admission and PDI, (2) use of AC/SED and PDI, and (3) the number of AC/SED drugs and PDI. In all situations, we applied a multivariable logistic regression model to estimate the odds ratio (OR) with 95% confidence intervals (CIs). Variables for the regression model was selected by using a directed acyclic graph created in DAGitty v3.0 causal diagram,[36,37] see Supplementary material S2.

2.8 | Data access and ethical approval

The regional ethics committee and the Norwegian Data Protection Authority approved the study (REK-reference: 2014/2182, Project number 25995).

3 | RESULTS

The study population comprised 86 509 patients of whom 1715 comprised the subpopulation with geriatric IS. The mean number of drugs dispensed 120 days before admission was 7.1 for the total study population and for the geriatric subgroup. In the total study population, 24.6% were discharged to an institution, compared with 42.5% in the geriatric subgroup. Study population characteristics are presented in Table 1.

3.1 | Use of AC/SED drugs and DBI

In the total study population, 39 275 patients (45.4%) were exposed to at least one AC/SED drug, compared to 900 patients (52.5%) in the geriatric subgroup. Mean DBI was 0.48 (range 0–6.04, SD = 0.68) for the total study population and 0.55 (range 0–4.65, SD = 0.71) for the geriatric subgroup. Mean individual contributions of SED and AC drugs to the DBI is given in Table 1.

3.2 | Associations AC/SED drugs and PDI

The logistic regression model exploring the association between DBI, use of AC/SED and the number of AC/SED drugs, and PDI is outlined in Table 2. For the full model, including all covariates, please see Supplementary material S3. From the scatterplot, we observed a change in the slope and identified the knot point at DBI = 2.45. Consequently, for the total study population, the DBI variable was split in two continuous variables comprising 37 371 patients with DBI < 2.45 and 1832 patients with DBI ≥ 2.45, while for the geriatric subgroup 855 patients had DBI < 2.45 and 45 patients had DBI ≥ 2.45. A DBI increase of one unit significantly increased the odds of PDI in the total study population by OR 1.11 (95% CI 1.07–1.15) and 1.08 (95% CI 1.04–1.13) for DBI < 2.45 and DBI ≥ 2.45, respectively. A similar effect was not identified in the geriatric subgroup, see Table 2.

When the splined variables were replaced with the use of AC/SED drugs (yes/no) per patient, the ORs changed slightly for the total study population to 1.09 (95% CI 1.05–1.14) and for the geriatric subgroup to 1.11 (95% CI 0.86–1.42). Replacing the splined variables with the number of AC/SED-drugs combined had a similar effect, that is, changing the ORs for the total study population to 1.07 (95% CI 1.05–1.09) and for the geriatric subgroup to 1.06 (95% CI 0.93–1.19). Replacing the splined variables with DBI for the AC component and number of AC drugs in use increased the OR for the study population, with OR 1.23 (95% CI 1.15, 1.31) and OR 1.13 (95% CI 1.08, 1.17), respectively. Replacing with SED component/number of drugs slightly decreased the associations in the study populations. In all situations, the results remained only significant for the total study population.

TABLE 1 Characteristics of the total study population and the geriatric subgroup.

Patient characteristics	Total population $N = 86\,509$	Geriatric subgroup $n = 1715$
Age (years), mean (SD)	81.5 (7.0)	85.0 (6.6)
Min, max	70, 105	70, 101
Female, *n* (%)	48 964 (56.6)	1092 (63.7)
Discharged to institution, *n* (%)	21 281 (24.6)	729 (42.5)
Charlson Comorbidity Index score, mean (SD)	2.0 (1.8)	1.9 (1.8)
Min, max	0, 15	0, 14
No. of hospital stays previous year, mean (SD)	3.6 (7.8)	3.0 (6.1)
Min, max	0, 206	0, 162
No. of drugs pre-index stay, mean (SD)	7.1 (4.0)	7.1 (3.8)
Min, max	1, 35	1, 28
Discharge diagnosis,[a] *n* (%)		
Diseases of the circulatory system	21 281 (24.6)	405 (23.6)
Diseases of the respiratory system	11 246 (13.0)	226 (13.2)
Fractures	8737 (10.1)	22 (1.3)
Symptoms/signs/abnormal findings	8132 (9.4)	206 (12.0)
Diseases digestive system	7613 (8.8)	45 (2.6)
Diseases genitourinary system	4845 (5.6)	146 (8.5)
Mental and behavioral disorders	1298 (1.5)	226 (13.2)
Length of hospital (index) stay, mean (SD)	5.3 (6.0)	8.1 (6.7)
Min, max	1, 132	1, 72
Anticholinergic and sedative drugs, *n* (%)		
0	47 234 (54.6)	815 (47.5)
1	22 492 (26.0)	496 (28.9)
2	10 122 (11.7)	232 (13.5)
≥3	6661 (7.7)	173 (10.1)
Anticholinergic drugs, mean (SD)	0.19 (0.47)	0.23 (0.52)
Min, max	0, 5	0, 3
Sedative drugs, mean (SD)[b]	0.58 (0.88)	0.67 (0.91)
Min, max	0, 8	0, 6
Drug Burden Index, mean (SD)	0.48 (0.68)	0.55 (0.71)
Min, max	0, 6.04	0, 4.65
Drug Burden Index AC component, mean (SD)	0.11 (0.28)	0.13 (0.30)
Min, max	0, 3.11	0, 2.17
Drug Burden Index SED[b] component, mean (SD)	0.37 (0.56)	0.42 (0.59)
Min, max	0, 5.65	0, 4.08

[a]Most frequent registered.
[b]Includes drugs with sedative properties only, see Supplementary material S1,

4 | DISCUSSION

This is the first study to describe the prevalence of AC/SED drugs at hospital admission in Norwegian community-dwelling older patients and investigate its association with PDI following an acute hospital stay. We identified high prevalence of AC/SED drugs (45%), and even higher in the geriatric subgroup (52%). We also observed a statistically significant association between AC/SED drug use and PDI, independent of which approach used, where number of AC drugs had the strongest association with PDI. In the geriatric subgroup, this association was not observed.

TABLE 2 Multivariable logistic regression presenting the association (odds ratio, OR) between all drug burden exposure variables, and the outcome postdischarge institutionalization (PDI) for the total population ($n = 86\ 509$) and the geriatric subgroup ($n = 1694$).

	Total population		Geriatric subgroup[a]	
Exposure variables[b]	**OR[c]**	**(95% CI)**	**OR[d]**	**(95% CI)**
Drug Burden Index (DBI)				
Score <2.45 (Spline1)	1.11	(1.07–1.15)	0.99	(0.79–1.23)
Score ≥2.45 (Spline2)	1.08	(1.04–1.13)	1.21	(0.94–1.55)
Only AC component	1.23	(1.15–1.31)	1.08	(0.72–1.61)
Only SED[e] component	1.07	(1.03–1.10)	1.07	(0.87–1.32)
Use of drug with AC/SED properties (yes/no)	1.09	(1.05–1.14)	1.11	(0.86–1.42)
Number of drugs				
With AC/SED properties	1.07	(1.05–1.09)	1.06	(0.93–1.19)
With AC properties	1.13	(1.08–1.17)	1.03	(0.81–1.30)
With SED[e] properties	1.05	(1.02–1.07)	1.06	(0.92–1.22)

[a]OR could not be calculated for 21 patients since all geriatric patients with two categories of discharge diagnoses had same outcome = predicted failure perfectly, see Supplementary material S3.
[b]The model adjusts for discharge diagnoses according to the ICD10 system, age, number of hospital stays previous year, length of index hospital stay, number of drugs pre-index stay, and Charlson Comorbidity Index score calculated from reimbursement codes of drugs used according to the Norwegian Prescription Database.
[c]Pseudo $R^2 = 0.1418$.
[d]Pseudo $R^2 = 0.1342$.
[e]Includes drugs on the list of drugs with sedative properties only see Supplementary material S1.

4.1 | Principal findings and implications

Although the prevalence of AC/SED drug use in our study was high, it is comparable to other studies reporting prevalence from 32% to 62%.[24,38–40] One reason for the considerable variation between studies, may be that no international consensus exists concerning which drugs to be defined as AC/SED drugs. Consequently, comparisons between studies should be done with caution. Nevertheless, our findings confirm a high drug burden amongst these older patients.

We identified significant associations between AC/SED drug use at hospital admission and PDI which indicate that an acute hospital admission is an opportunity to initiate actions to reduce drug burden in older patients, as also suggested by others.[41] Surprisingly, the ORs related to AC drugs were closer to one in the geriatric subgroup compared to the total study population. The associations between AC/SED drug exposure and the outcomes were not statistically significant in the geriatric subgroup, which is probably explained by the much smaller sample size. Potential differences in effect size of AC exposure on PDI between the populations on the other hand, is difficult to explain from our data. Our results may be influenced by the shift towards extended use of home care services in Norway to keep older people home-dwelling for a longer time before institutionalization. A higher proportion (almost 70% increase) of patient from the geriatric subgroup experienced PDI compared to the total study population, see Table 1, which is contrary to previous findings.[42] It is likely this subgroup of patients experienced age related functional decline to a point where admission to a geriatric ward function as an entry point for institutionalisation. Nevertheless, our focus on reducing drug burden in older hospitalized patients should remain, as also pointed out by Egberts et al.[43]

We found significant relationships between AC/SED drugs and PDI, independent whether we applied DBI, the AC/SED components of DBI, the dichotomous variable "using an AC/SED drug or not," or the number of AC/SED drugs used, both combined and separately. The AC component had the highest OR of 1.23, however, the number of AC drugs in use was more sensitive for PDI, with OR of 1.13 per AC drug, since a one unit increase in DBI require the use of at least two DBI-drugs, as explained in Section 2.4. Focusing on the burden from AC drugs to decrease the risk of PDI is in line with the findings from Egberts et al., who also found a significant association between number of AC drugs and PDI (OR = 1.38).[43] Combined, these findings from retrospective studies suggest performing prospective interventional studies to unravel the effect of reduction in AC and/or SED burden on PDI.

The complexity of the DBI, involving preparations, calculations, and the implications of the scores, challenges the comprehension of the DBI and the application as a clinical tool. In addition, our findings suggest that reducing the *number* of AC/SED drugs have a stronger impact on the risk of PDI in older acutely hospitalised patients compared to applying the DBI and is also easier to apply.

4.2 | Strengths and limitations

The main strength of this study is the use of national high-quality registries with complete data on both hospitalizations and drug dispensing. This enables the inclusion of all relevant hospitalizations and drug dispensing in the population and eliminates selection and recall bias normally associated with observational designs. The fact that all Norwegian citizens can be identified with a unique personal identification

number enables linking between databases and the completeness of data.

As the DBI variable is an index, we believe that splining DBI and keeping it as a continuous variable in our regression analysis is a more appropriate choice than using DBI as a categorical independent variable.[16,22,44] This is also in line with the development of the DBI.[15] Given the variations in how to estimate individual AC/SED drug exposure (especially for pharmacy database exposure calculations), which impacts the prevalence of these drugs and the magnitude of calculated DBI, it seems unlikely that the same cut off values or intervals should apply to all DBI-data.

AC/SED exposure was defined applying dispensing data from pharmacy records. Prevalence is affected by drugs included and choice of look back period, which affects the sensitivity. To appropriately define drug use, we chose to use the legend approach that provides good estimates of drug exposure at a fixed time point.[32] This has not previously been used for daily dose estimates in DBI studies. On the other hand, to determine legend duration by using the daily dispensed unit strength of drugs multiplied by number of daily administrations, is a more reliable estimate of drug exposure than Defined Daily Doses (DDD).[45] This approach also gives individual DBI-scores mirroring the clinical setting, reflecting known drug-unit strengths. Due to expected variability in non-adherence patterns for the drugs included as AC/SED-drugs, especially for psychotropic drugs,[45,46] we chose not to add grace periods.[47] By applying dispensing data from pharmacies, an underestimation of AC/SED exposure may have occurred, as only drugs dispensed from pharmacies are included, and not over the counter drugs and herbal medicines.[27] Neither do we have information on hospital-dispensed drugs and consequently no adjustments in exposure to AC/SED drugs during the hospital stay. This may have underestimated drug exposure, as we know that drug use may increase during hospitalisation in older patients,[48] that number of potentially inappropriate medications not necessarily are decreased,[48] and that hospital stays may increase the exposure to AC/SED drugs.[49]

5 | CONCLUSIONS

The use of AC/SED drugs is highly prevalent in older patients before acute hospital admissions, and significantly associated with post-discharge institutionalization (PDI) in the study population although not in the subgroup of patients admitted to geriatric wards. Applying the number of AC/SED drugs, or just using or not using AC/SED drugs gave similar associations with PDI compared to applying the drug burden index (DBI). The strongest association was found for number of AC drugs in use. This indicates that a clinical approach to prevent PDI in older patients could simply be to focus on reducing the number of AC drugs. This should be further explored.

AUTHOR CONTRIBUTIONS

Kjerstin Havnes: Conceptualization; data curation; formal analysis; methodology; visualization; writing – original draft; writing – review and editing. **Kristian Svendsen:** Conceptualisation; data curation; formal analysis, methodology; supervision; writing – original draft; writing – review and editing. **Jeanette Schultz Johansen**: Data curation, writing – original draft; writing – review and editing. **Anne Gerd Granås:** Writing – original draft; writing – review and editing. **Beate H Garcia:** Visualization; Writing – original draft; Writing – review and editing. **Kjell H Halvorsen**: Conceptualisation; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are subject to restrictions. Patient privacy requirements according to Norwegian law prevents sharing of individual patient level data in public repositories.

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