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Drug burden index and its association with hip fracture among older adults: a national population-based study

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Abstract.**Background.**

The Drug Burden Index (DBI) calculates the total sedative and anticholinergic load of prescribed medications, and is associated with functional decline and hip fractures in older adults. However, it is unknown if confounding factors influence the relationship between the DBI and hip fractures. The objective of this study is to evaluate the association between the DBI and hip fractures, after correcting for mortality and multiple potential confounding factors.

Methods.

A competing risk regression analysis conducted on a prospectively recruited New Zealand community-dwelling older population who had a standardized (interRAI) assessment between 1 September 2012 and 31 October 2015, the study's end date. Outcome measures were survival status, and hip fracture, with time-varying DBI exposure derived from 90-day time-intervals. The multivariable competing risk regression model adjusted for a large number of medical comorbidities and activities of daily living.

Results.

Among 70,553 adults assessed, 2,249 (3.2%) experienced at least one hip fracture, 20,194 (28.6%) died without experiencing a fracture, and 48,110 (68.2%) survived without a fracture. The mean follow-up time was 14.9 months (range: 1 day, 37.9 months). The overall DBI distribution was highly skewed, with median time-varying DBI exposure ranging from 0.93 (Q₁=0.0, Q₃=1.84) to 0.96 (Q₁=0.0, Q₃=1.90). DBI was significantly related to fracture incidence in unadjusted (p<0.001) and adjusted (p<0.001) analyses. The estimated subhazard ratio was 1.52 (95% confidence interval: 1.28, 1.81) for those with DBI>3 compared with those with DBI=0 in the adjusted analysis.

Conclusions.

In this study, increasing DBI was associated with a higher likelihood of fractures after accounting for the competing risk of mortality and adjusting for confounders. The results of this unique study are important in validating the DBI as a guide for medication management and it could help reduce the risk of hip fractures in older adults.

Key words. Polypharmacy, medications, RAI, falls

Introduction.

Hip fractures in frail older people often require complex care and may lead to loss of independence. After hip fractures, older people often require aged residential care, which is costly to the patient and the health system.(1) Twenty to thirty percent of older people with hip fractures die within 12 months of their injury.(2) If surgery is undertaken, patients frequently experience significantly reduced hip function and mobility beyond 12 months.(3) Approximately 90% of hip fractures in older people are a direct result of a fall,(4) consequently clinicians must prioritize initiatives that help reduce the risk of falls and subsequent hip fractures in older people. Polypharmacy can increase the risk of falls in older people.(5) Research has highlighted that medications with sedative and anticholinergic properties significantly increase the risk of falls in the older populations.(6) While there are many benefits of modern pharmacological interventions,(7) and polypharmacy may at times be entirely appropriate, deprescribing, particularly the withdrawal of some sedative and anticholinergic drugs may result in clinical benefit for some individuals, such as an improvement in physical function.(6,8,9) The Drug Burden Index (DBI) was developed as a pharmacological risk assessment tool.(10) Unlike other tools that identify potentially inappropriate medication use,(11,12) the DBI calculates the cumulative sedative and anticholinergic load of an individual's prescribed medications.(13) Previous work has highlighted the relationship between a high DBI score and functional decline in older populations, and falls and fractures.(6,9,14,15) Nonetheless, the association of the DBI with hip fractures has not yet been explored at a population level. Our national study examined the relationship between DBI and hip fractures in the frail elderly after adjusting for multiple possible confounders within the New Zealand International Resident

Assessment Instrument (interRAI) dataset. We linked pharmaceutical, mortality and fracture data with anonymized interRAI-Home Care data (interRAI-HC).

METHODS

We conducted a competing-risk regression analysis on a prospectively recruited national cohort.

Participants

The participants included home-based people aged 65 years and older who had an interRAI-homecare (HC) assessment between 1 September 2012 and 31 October 2015, the study's end date, and who consented to their data being used for planning and research purposes. In New Zealand, the interRAI-HC instrument is used for all community care assessments of older people being considered for publicly-funded long-term community services or aged residential care in New Zealand.(16)

Procedure

A detailed account of the interRAI-HC assessment instrument and procedure within New Zealand has been described previously.(16) In brief, the standardized interRAI-HC instrument is used to conduct all community care assessments on older people needing publicly funded long-term community services or aged residential care. Individuals are referred by a health practitioner to have their needs assessed by one of the 1,800+ trained interRAI assessors. Assessors visit clients in their own home to produce individualized care-plans according to a standardized protocol. Participants are explicitly asked if they consent to their de-identified interRAI-HC information being used for planning and research purposes. All data are directly entered into an electronic

interRAI-HC database that is maintained by New Zealand's Technical Advisory Services (TAS; <http://centraltas.co.nz>). With approval consented data are released by TAS through the Ministry of Health.

Instrument and primary measures

The interRAI-HC 9.1 instrument (© interRAI Corporation, Washington, D.C., 1994-2009), modified with permission for New Zealand, is used under license to the New Zealand Ministry of Health (www.interrai.co.nz). It is composed of 236 questions, which form 27 standardized instruments, and yields internationally valid and reliable scales.(16,17) InterRAI-HC information is stored electronically and is linked to the National Health Index (NHI) numbers using encryption for data security. The NHI is a unique identifier that is assigned to every person who uses health and disability support services in New Zealand.

The fracture data were extracted from the Ministry of Health's National Minimum Dataset (NMDS),(18) released with encrypted NHI numbers for all consenting interRAI-HC participants. Fractures included: ICD-10-AM codes S720 – fracture of head and neck of femur; S721 – pertrochanteric fracture; S722 – subtrochanteric fracture of femur; S723 – fracture of shaft of femur; S724 – fracture of lower end of femur; S728 – other fracture of femur; and S729 – unspecified fracture of femur. Only the first documented fracture and date of that fracture were used in the study.

Survival status and date of death data were extracted from the National Mortality Collection Register (NMCR), also held by the Ministry of Health,(19) and released with encrypted NHI numbers for all consenting interRAI-HC participants.

Pharmaceutical information, including medicine names and prescription dates, were captured by the national collections of prescription use (Pharmaceutical Collection), jointly owned by the Ministry of Health and PHARMAC, and linked through encrypted NHI numbers. The Drug Burden Index (DBI) exposure was calculated for medicines with anticholinergic and sedative properties (see Table S1 in the supplementary materials) dispensed from 1 September 2011 through 31 October 2015. The drug burden attributable to each anticholinergic or sedative medicine was calculated using the equation:

$$\text{Drug Burden Index} = \sum_0^{90} D / (D + \delta)$$

where D is the daily supply (or dose) taken by the individual and δ is the minimum efficacious dose. As pharmaceutical prescribing changes over time, each participant's DBI exposure was treated as a time varying variable, partitioned into 90-day intervals over their study duration, beginning with the 90 days pre-interRAI-HC assessment. The cumulative DBI exposure for each 90-day interval was calculated using the principles trapezoidal area under the curve as described in the original study (20). Area under the curve for drug burden was derived by calculating the drug burden index for each drug multiplied by the time of exposure (90 days). It was assumed that any medicines dispensed during the 90-day period were taken for the full 90 days. Dispensing for more than 90 days was truncated to 90 days. The DBI was then partitioned into four groups, namely: (i) $\text{DBI}=0$; (ii) $0 < \text{DBI} \leq 1$; (iii) $1 < \text{DBI} \leq 3$; and, (iv) $\text{DBI} > 3$. $\text{DBI}=0$ is the most numerous and covers participants who do not take the anticholinergic and sedative drugs. In smaller studies, $\text{DBI}=1$ is often used as a threshold value. But here, with a large sample, $\text{DBI}=3$ captures the most extreme drug burdens among participants. These thresholds have both clinical and statistical utility, as demonstrated previously. (14)

Demographic and potentially confounding measures

Similar to previous published studies, age, sex, ethnicity, body mass index (BMI), cognitive performance, dementia, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), depression, diabetes mellitus, urinary incontinence, alcohol consumption, smoking status, hearing status, vision status, fatigue, mobility, wandering, seasonality, and supplementation of bisphosphonates, vitamin D, and calcium were all utilized as potential confounding factors. Apart from the supplementations, all measures arose from the interRAI-HC assessment. The bisphosphonates, vitamin D, and calcium supplementation indications were also derived from the Pharmaceutical Collection and were treated as time varying confounders, as was season, over 90-day intervals. All variable specification details appear in the supplementary materials Table S2.

Statistical analysis

Reporting of analyses were informed by the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (www.strobe-statement.org). The interRAI-HC, NMDS, and NMCR databases were deterministically matched using participants' encrypted NHI numbers. Where an individual had more than one interRAI-HC assessment, only the first assessment was utilized. Several interRAI-HC variables were re-classified, as given in the supplementary material, with contiguous categories combined when cell sizes were relatively small. Descriptive statistics of all variables of interest were then reported. Competing risk regression models were next employed, treating fracture as the primary event of interest and death as a competing event.

Initially unadjusted models were investigated, followed by a multivariable model with inclusion of demographic and potential confounding variables. Exploring whether a differential influence of sex and age might have on the relationship between DBI grouping and fracture likelihood, the

multivariable competing risk regression model was repeated with the addition of DBI grouping×sex and DBI grouping×age grouping interaction terms. Rather than using bivariable analyses to screen risk factors, in the spirit of Sun and colleagues,(21) all candidate variables were included in the multivariable model regardless of their statistical significance. Subhazard ratios (SHRs) and associated 95% confidence intervals (CIs) were reported, and Wald's type III χ^2 test was used to determine the significance of variables within the regression. The population attributable fraction (PAF) was used to estimate the proportional reduction in fracture numbers that would occur if exposure to DBI at baseline was reduced to an alternative ideal exposure scenario (DBI=0), and 95% CIs derived using computer simulation.(22) All analyses and graphics were performed using Stata SE version 14.1 (StataCorp, College Station, TX, USA), and $\alpha=0.05$ defined statistical significance.

Table S3 in the supplementary materials gives the observed distribution and regression estimates for the unadjusted and multivariable models for all considered variables. Exploring whether a differential influence of sex and age might have on the relationship between DBI grouping and fracture likelihood, the multivariable competing risk regression model was repeated except with the addition of DBI grouping×sex and DBI grouping×age grouping interaction terms.

Ethics

Clearance for this study was approved by the Ministry of Health's Health and Disability Ethics Committees (14/STH/140), and it only includes de-identified data for people consenting to its use for planning and research purposes.

RESULTS

The study cohort included 72,193 individuals aged ≥ 65 years (Figure 1). After exclusions, there were 70,553 eligible individuals. The average age at assessment was 82.7 years (range: 65, 106 years; Table 1). Approximately two-thirds of those assessed were female with a higher proportion of females than males alive at the end of the study period. Most people (88.5%) were New Zealand European and approximately half the individuals were living alone. The average follow-up time was 14.9 months after the interRAI assessment (range: 1 day, 37.9 months), totaling 87,671 person-years of follow-up data.

Fractures and mortality

By the study end-date, 2,249 (3.2%) participants had experienced at least one fracture, 20,194 (28.6%) had died without experiencing a fracture, and 48,110 (68.2%) were alive and without a fracture (Figure 1). The median time from assessment to the first fracture event was 8.5 months ($Q_1=3.7$, $Q_3=15.5$ months), and from assessment to death (without fracture) was 6.9 months ($Q_1=2.2$, $Q_3=15.0$ months). Table 1 also includes the demographic profile of participants by fracture status, and shows important distributional differences. Fracture rates increased with increasing age, females had relatively higher rates than males, New Zealand Europeans had relatively higher rates than other ethnic classifications, as did participants who were widowed, or who lived alone or with a child (but not a spouse or partner).

Drug Burden Index (DBI)

The distribution DBI values was highly skewed (see Figure 2). In the pre-assessment 90-day period, 29,111 (41.3%) participants had a DBI equaling 0; taking no medications that contributed

to the index, 20,791 (29.5%) had $0 < \text{DBI} \leq 1$; 16,600 (23.5%) had $1 < \text{DBI} \leq 3$; and, 4,051 (5.7%) had $\text{DBI} > 3$. The numbers of participants available within the study at baseline and at time-points after baseline, together with the median (Q_1 , Q_3) DBI exposure score of these participants is presented in Table 2. Median DBI scores remained low throughout the study period. The correlation in DBI scores between contiguous 90-day intervals ranged from 0.68 (between pre- and 0-89 days post-assessment DBI scores) to 0.85 (between 900-989 days and 990-1079 days post-assessment DBI scores) meaning subjects experienced a relatively constant rate of anti-cholinergic drug use over time.

Unadjusted analyses

Treating DBI as a time-varying variable, the unadjusted competing-risk regression model yielded a significant relationship between DBI grouping and fractures over time ($p < 0.001$), with estimated subhazard ratios (SHRs) and associated 95% CIs presented in Table 3. There appeared to be a dose-response relationship between estimated SHRs, with increasing drug burden associated with a higher likelihood of fractures, after accounting for the competing increasing death rate. Figure 3a gives the cumulative incidence of fractures over time by DBI groupings from this analysis.

Adjusted analyses

After multivariable adjustment, the DBI grouping remained significantly related to fracture incidence ($p < 0.001$) (Table 3). Table S3 in the supplementary materials gives the observed distribution and regression estimates for the bivariable and multivariable models for all considered variables. The apparent dose-response relationship between DBI grouping and fracture incidence observed in the unadjusted analysis remained in the multivariable analysis; indeed, it appeared

stronger than in the unadjusted model. Figure 3b, which also depicts the cumulative incidence of fractures over time by DBI groupings visually highlights the strength of this association. Note, in this graphic all included demographic and potential confounder variables were assigned their reference values (as given in Tables 3 and S3 of the supplementary materials). However, no evidence of DBI grouping effect modification was seen by sex ($p=0.53$) or age grouping ($p=0.42$).

Population attributable fraction

The population attributable fraction (PAF) derived from the adjusted subhazard estimates and the observed baseline DBI distribution (Table 3), assuming a counterfactual population level of DBI=0, yielded PAF=12.3% (95% CI: 8.2%, 61.1%).

Discussion

In this national study, higher DBI scores were associated with an increased likelihood of hip fractures after accounting for the competing risk of mortality. This is consistent with previous observations of the association of DBI with falls in the total New Zealand population aged over 65 years, (9) and in residents of Australian aged care facilities.(15) It is also consistent with the large body of evidence demonstrating an association between different types of drugs with anticholinergic and sedative effects and falls and fractures.

A strength of this study was that after adjusting for a suite of potential confounders, the dose response relationship between DBI scores and fractures increased. Unlike most studies that have demonstrated an association between DBI and adverse outcomes at a population level, (20, 23,24) this study controlled for a wide range of potential confounders including baseline function and medical comorbidities.

A number of studies support the validity of the DBI as an aid to prescribing.(6,9,10) One reported a relationship between falls and fractures and specific medication groups such as psychotropic drugs.(15) Another study investigated the association between the DBI and physical function in a population of aged residential care residents in Australia.(15)That cohort's mean age was slightly greater than our community based study. In that study, sedative exposure was significantly associated with poor balance (OR 1.57, 95% CI 1.08-2.27), a known risk factor for falls in older populations.(15) Poorer physical function has also been reported associated with the increased use of sedative and anticholinergic medications as defined by the DBI rather than polypharmacy per se.(13) An important association between both long and short acting benzodiazepines and falls was found in a study of older people living in long-term residential care, although the cumulative effect of other sedative and anticholinergic medications was not considered.(25) Other reported research has also highlighted the link between narcotic analgesics and risk of fractures,(26) and the association between SSRI use and falls and hip fractures in the older populations.(27-30) Reducing polypharmacy and identifying at risk medications is generally important. Up to 50% of older people have exposure to medications with anticholinergic properties.(31) These data indicate that the total anticholinergic and sedative load should be considered particularly in the context of reducing fractures rates in the frail older population.

Ours is the first study to examine the relationship between hip fractures in older people and the DBI at a population level. The rich source of data made available through the interRAI-HC data base in New Zealand, linked to pharmaceutical, fracture and mortality data allowed us to include confounders that have previously been unavailable to other population based studies of the most frail and vulnerable older people.(16,32)

Limitations

The New Zealand interRAI-HC identifies older people who are most frail and vulnerable and who are therefore most likely to be at risk of falls and fractures. We acknowledge, also, that in our study the period between individual interRAI-HC assessments and any subsequent fracture varied between participants, and so any variance in Activities of Daily Living (ADL) function or cognition may not always have been captured. Although all dispensed medications in the study period were utilized, there was no way of ascertaining whether they had always been consumed. Furthermore, non-prescription medications with anticholinergic and sedative effects, such as some antihistamines and mild opioids, were not captured by our data sets, so could not be included in the DBI calculations. We adjusted for many potential important confounders including congestive heart failure; however, we did not have detailed information on every potential confounder, such as musculoskeletal pain, and it is possible that residual confounding remains. The interRAI-HC assessment involves a significant degree of self-reporting, which may result in some inconsistencies, for example when the individual has a degree of cognitive impairment. However, assessments are often completed in the company of a spouse or other family member and primary care doctors are consulted to verify the information provided and clarify unclear details. It is important to note that the absolute DBI exposure may be higher in longitudinal studies compared to cross sectional studies because we calculate cumulative (multiplied by time) drug exposure in longitudinal studies. As shown in this study, higher exposures are associated with worse clinical outcomes, but we could not extrapolate information on the cut-offs or degree of DBI exposure. Misclassification of drug exposure is inherent in pharmacoepidemiological studies, and in this study it was difficult to discern regular versus prn medications from dispensed data extracted from the national pharmaceutical collections.

Conclusion

This national study demonstrated that increasing exposure to anticholinergic and sedative medications is significantly associated with hip fractures in frail community dwelling older people in New Zealand. The Drug Burden Index may be useful as a risk assessment tool, helping clinicians to review prescribing for older patients. Exposure to anticholinergic and sedative medicines is a potentially reversible contributor to hip fractures, which cause significant morbidity and mortality for older people, and major costs of the health and aged care services.

Conflict of interest statement. The named authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Table 1. Demographics of eligible participants overall (n=70,553), and partitioned by outcome.

	Alive, no fracture			First event			
	Total	by end-date		Fracture		Died	
	n	n	(%)	n	(%)	n	(%)
<i>Age (years)</i>							
65-74	12,175	9,124	(74.9)	174	(1.4)	2,877	(23.6)
75-84	28,999	20,656	(71.2)	820	(2.8)	7,523	(25.9)
85-94	27,048	17,131	(63.3)	1,120	(4.1)	8,797	(32.5)
95+	2,331	1,199	(51.4)	135	(5.8)	997	(42.8)
<i>Sex^a</i>							
Female	43,048	30,945	(71.9)	1,569	(3.6)	10,534	(24.5)
Male	27,501	17,162	(62.4)	680	(2.5)	9,659	(35.1)
<i>Ethnicity</i>							
European	62,436	42,257	(67.7)	2,134	(3.4)	18,045	(28.9)
Māori	3,814	2,638	(69.2)	41	(1.1)	1,135	(29.8)
Pacific	2,187	1,622	(74.2)	26	(1.2)	539	(24.6)
Other	2,116	1,593	(75.3)	48	(2.3)	475	(22.4)

Marital status

Married/civil union/de facto	27,400	18,520	(67.6)	771	(2.8)	8,109	(29.6)
Widowed	34,194	23,292	(68.1)	1,258	(3.7)	9,644	(28.2)
Divorced/separated	5,144	3,685	(71.6)	133	(2.6)	1,326	(25.8)
Never married	3,235	2,235	(69.1)	71	(2.2)	929	(28.7)
Other	580	378	(65.2)	16	(2.8)	186	(32.1)

Residential arrangements: living with^b

Spouse/partner only	22,343	15,086	(67.5)	621	(2.8)	6,636	(29.7)
Spouse/partner and other(s)	2,396	1,598	(66.7)	60	(2.5)	738	(30.8)
Alone	34,973	24,334	(69.6)	1,215	(3.5)	9,424	(26.9)
Child (not spouse/partner)	7,676	4,992	(65.0)	263	(3.4)	2,421	(31.5)
Other relative(s)	1,729	1,184	(68.5)	49	(2.8)	496	(28.7)
Non-relative(s)	1,434	915	(63.8)	41	(2.9)	478	(33.3)

Note: ^a4 observations missing; ^b2 observations missing. See Table S3 of the Supplementary materials for details of demographic and potentially confounding variables by outcome at the study's end date.

Table 2. Numbers of people remaining at risk of hip fracture and/or death and their median (Q1, Q3) DBI exposure score.

Time after assessment (days)	n	(%)	median ^a	DBI exposure (Q1, Q3)
Baseline	70,553	(100.0)	0.93	(0.0, 1.81)
90	59,192	(83.9)	0.94	(0.0, 1.83)
180	51,303	(72.7)	0.93	(0.0, 1.81)
270	44,669	(63.3)	0.93	(0.0, 1.81)
360	39,090	(55.4)	0.93	(0.0, 1.82)
450	33,280	(47.2)	0.93	(0.0, 1.83)
540	27,384	(38.8)	0.93	(0.0, 1.84)
630	22,129	(31.4)	0.93	(0.0, 1.84)
720	17,429	(24.7)	0.94	(0.0, 1.85)
810	12,162	(17.2)	0.94	(0.0, 1.86)
900	7,649	(10.8)	0.94	(0.0, 1.87)
990	4,351	(6.2)	0.95	(0.0, 1.90)
1,080	1,871	(2.7)	0.96	(0.0, 1.90)

^aDBI values measured over time

Table 3. Distribution of DBI groupings for the pre-assessment period by outcome at the study’s end date, together with subhazard ratios (SHRs) and 95% confidence intervals (CIs) for the unadjusted and adjusted analyses.

	Alive, no fracture		First event		Unadjusted		Adjusted ^a	
	by end-date		Fracture	Died	SHR	(95% CI)	SHR	(95% CI)
	n	(%)	n (%)	n (%)				
DBI=0	20,274	(69.6)	893 (3.1)	7,944 (27.3)	1	(reference)	1	(reference)
0<DBI≤1	14,306	(68.8)	687 (3.3)	5,798 (27.9)	1.11	(1.00, 1.23)	1.12	(1.01, 1.24)
1<DBI≤3	11,051	(66.6)	544 (3.3)	5,005 (30.2)	1.24	(1.12, 1.38)	1.32	(1.18, 1.47)
3<DBI	2,479	(61.2)	125 (3.1)	1,447 (35.7)	1.28	(1.08, 1.52)	1.52	(1.28, 1.81)

^aAdjusted for: age, sex, ethnicity, body mass index (BMI), cognitive performance, dementia, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), depression, diabetes mellitus, urinary incontinence, alcohol consumption, smoking status, hearing status, vision status, fatigue, mobility, wandering, seasonality, and supplementation of bisphosphonates, vitamin D, and calcium

