The Association Between Drug Burden Index (DBI) and Health-Related Outcomes: A Longitudinal Study of the 'Oldest Old' (LiLACS NZ)

Cardwell, K., Kerse, N., Ryan, C., Teh, R., Moyes, S. A., Menzies, O., Rolleston, A., Broad, J., & Hughes, C. M. (2020). The Association Between Drug Burden Index (DBI) and Health-Related Outcomes: A Longitudinal Study of the 'Oldest Old' (LiLACS NZ). *Drugs and Aging*. https://doi.org/10.1007/s40266-019-00735-z

Published in:
Drugs and Aging

Document Version:
Peer reviewed version

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Running heading: LiLACS NZ: Drug Burden Index

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Acknowledgements

We thank all the participants and their whanau/families for their time and contribution to the principal study. The Rōpū Kaitiaki (Hone Kameta, Florence Kameta, Betty McPherson, Te Kaanga Skipper, Paea Smith, Laiana Reynolds) oversaw the project from feasibility and throughout recruitment. Elizabeth Robinson guided the biostatistical planning and Rudi Westendorp gave advice at the planning stages.

Abstract

Background: The prescribing of medications with anticholinergic and/or sedative properties is considered potentially inappropriate in older people (due to their side effect profile) and the Drug Burden Index (DBI) is an evidence-based tool which measures exposure to these medications. Life and Living in Advanced Age: a Cohort

Study in New Zealand (LiLACS NZ) is an on-going longitudinal study investigating the determinants of healthy ageing. Using data from LiLACS NZ, this study aimed to determine whether a higher DBI was associated with poorer outcomes (hospitalisation, falls, mortality and cognitive function and functional status) over 36-months follow-up.

Methods: LiLACS NZ consists of two cohorts: Māori (the indigenous population of New Zealand) were aged ≥80 years and non-Māori aged 85 years at the time of enrolment. Data relating to regularly prescribed medications at baseline, 12-months and 24-months, were used in this study. Medications with anticholinergic and/or sedative properties (i.e. medications with a DBI>0) were identified using the Monthly Index of Medical Specialities (MIMS) medication formulary, New Zealand. DBI was calculated for everyone enrolled at each time-point. The association between DBI at baseline and outcomes was evaluated throughout a series of 12-month follow-ups using negative binomial (hospitalisations and falls), Cox (mortality) and linear (cognitive function and functional status) regression analyses (significance $p<0.05$). Regression models were adjusted for age, gender, general practitioner (GP) visits, socioeconomic deprivation, number of medicines prescribed and one of the following: prior hospitalisation, history of falls, baseline cognitive function (3MS) or baseline functional status (NEADL).

Results: Full demographic data were obtained for 671, 510 and 403 individuals at baseline, 12-months and 24-months, respectively. Overall, 31%, 30% and 34% of individuals were prescribed a medication with a DBI>0 at baseline, 12-months and 24-months, respectively. At baseline and 12-months, non-Māori had a greater mean DBI (0.28 ±0.5 and 0.27 ±0.5, respectively) compared to Māori (0.16 ±0.3 and 0.18± 0.5, respectively). At baseline, the most commonly prescribed medicines with a DBI>0 were zopiclone, doxazosin, amitriptyline and codeine. In Māori, a higher DBI was significantly associated with a greater risk of mortality (at 36-months' follow-up), adjusted Hazard Ratio (95% Confidence Intervals [CIs]) 1.89 (1.11, 3.20) p=0.02. In non-Māori, a higher DBI was significantly associated with a greater risk of mortality (at 12-months' follow-up), adjusted Hazard Ratio (95% Confidence Intervals [CIs]) 2.26 (1.09, 4.70) p=0.03 and impaired cognitive function (at 24-months' follow-up), adjusted mean difference in NEADL score (95% CIs) 0.89 (-3.89, -0.41) p=0.02.

Conclusions: Using data from LiLACS NZ, a higher DBI was significantly associated with a greater risk of mortality (in Māori and non-Māori) and impaired cognitive function (in non-Māori). This highlights the importance of employing strategies to manage the prescribing of medications with a DBI>0 in older adults.

Key points

- The Drug Burden Index (DBI) is an evidence-based tool used to measure cumulative exposure to medications with anticholinergic and/or sedative properties.
- In Māori and non-Māori, a higher DBI was associated with a greater risk of mortality.
- In non-Māori, a higher DBI was associated with a greater risk of impaired cognitive function.

1.0 Background

Several studies using different tools indicate the prescribing of medications with anticholinergic and/or sedative properties as potentially inappropriate in older people, due to their side effect profile [1]–[8]. These side effects (e.g. reduced concentration, confusion, dry mouth, constipation, urinary retention, falls) may be even more problematic in the 'oldest old' (i.e. those aged ≥80 years), due to their increased vulnerability and risk of adverse drug reactions (ADRs) [9]. Consequently, various tools have been developed to specifically quantify 'anticholinergic medication burden' (defined as the cumulative effect of taking multiple medications with anticholinergic properties) [10] .

The Drug Burden Index (DBI) is an example of such a tool, which is used to quantify either anticholinergic or sedative medication burden, or both, in older people [11]. The DBI is an evidence-based tool which calculates medication burden using a pharmacological equation that incorporates drug dose and the principles of dose-response [12]. A recent systematic review determined it to be the most appropriate tool for use in research conducted within the 80+ population [13].

Several studies have investigated anticholinergic burden and its association with clinical outcomes. However, the majority of studies have been limited in their ability to predict health-related outcomes, due to either their cross-sectional design or short follow-up period [13]. Longitudinal studies track exposures (e.g. changes in prescribing patterns) and outcomes (e.g. frequency of falls) over time and may suggest cause-and-effect relationships [14]. Life and Living in Advanced Age: a Cohort Study in New Zealand (LiLACS NZ) is an on-going longitudinal study of ageing, the aim of which is to identify the determinants of healthy ageing for both Māori and non-Māori [15]. Māori are the indigenous population of New Zealand, accounting for approximately 16% of the total population living in New Zealand [16]. Research has shown that whilst Māori longevity has increased overtime, it has not yet matched that of non-Māori populations [17]. Preventable health disparities between indigenous and non-indigenous populations are prevalent internationally. Engagement of indigenous populations in health research is important to better understand existent disparities and enable the development of initiatives that will improve health outcomes for all [18]. However, it is acknowledged that such engagement is challenging due to differences in culture, beliefs and language [19]. Using data from LiLACS NZ, this study sought to determine the relationship between exposure to medications with anticholinergic and/or sedative properties, as measured by the DBI, and a predefined set of health-related outcomes (hospitalisations, falls, mortality cognitive function and functional status).

2.0 Methods

2.1 Study population

Data from LiLACS NZ were used in this current study. An overview of the principal study is described below, and full details of the study protocol are reported elsewhere [15]. The cohort consisted of Māori and non-Māori participants. Due to an observed disparity between Māori and non-Māori longevity, and because of the low numbers of Māori individuals residing in the area at the time of enrolment, Māori were eligible for inclusion if aged between 80-90 years and non-Māori if aged 85 years in 2010 [15]. Baseline data collection (which commenced in 2010) consisted of a standardised questionnaire (interview), a health assessment and a review of general practitioner (GP) medical records. Medication data (relating to prescribed medicines, over-the-counter

[OTC] medicines and *rongoā* [Māori] medicines) were collected during the interview by review of medicine container labels, including drug name, daily dose prescribed and frequency [15]. Rongoā medicines are native plant remedies used to treat colds, flu, gastrointestinal problems, aches and pains. They form an integral part of the traditional Māori healing system and are used in conjunction with physical and spiritual healing therapies [20]. Diagnoses of chronic conditions were ascertained by self-report during the interview and, at baseline only, study nurses or GP medical staff verified these conditions with GP records [21]. A health assessment was completed at each time-point, it consisted of a number of functional (e.g. cognitive function and functional status) and clinical (e.g. blood glucose and blood pressure) tests, and socioeconomic deprivation was evaluated using the New Zealand Deprivation Index [22].

2.2 Calculation of anticholinergic and sedative medication burden

The DBI measures older adults' exposure to medicines with anticholinergic or sedative properties; i.e. $DBI=DB_{AC}+DB_S$, where DB_{AC} represents the medication burden contributed by anticholinergic medications and DB_S represents the medication burden contributed by sedative medications [11]. The DBI for each medication is calculated using the following equation;

$$\boldsymbol{DBI=D/(DR_{50}+D)}$$

where 'D' represents the prescribed daily dose and 'DR_{50}' represents the daily dose required to achieve 50% of the maximal anticholinergic and/or sedative effect; estimated as the minimum daily dose (MDD) of each medication [11]. Total, or cumulative, DBI is calculated through summation of scores associated with each medication.

Medications with anticholinergic and/or sedative properties (i.e. medications with a DBI>0) were identified using the Monthly Index of Medical Specialities (MIMS) medication formulary, New Zealand [23]; this resource was also used to define the MDD associated with each medication. In accordance with Hilmer et al. [11], medications with both anticholinergic and sedative properties were classified as anticholinergic. The following medications were excluded from the DBI calculation: topical formulations, inhaled formulations and medications taken on an 'as needed' basis. Rongoā medicines were also excluded from the DBI calculation as the anticholinergic and sedative properties of these medicines have not been established. Medications with a DBI>0 were categorised according to the World Health Organisation Anatomical Therapeutic Chemical Classification system [24] to permit identification of the specific medication classes prescribed. Using medication data collected at baseline, 12-months and 24-months, each participant had their total DBI calculated (by summation of the DBI associated with each medication they were prescribed, using Microsoft® Excel) at each time-point.

2.3 Outcomes measured

Outcomes (all-cause hospitalisations, falls, mortality, cognitive function and functional status) were evaluated at 12-months', 24-months' and 36-months' follow-up during the face-to-face interview and health assessment. These outcomes were chosen as they are most commonly affected by medications with anticholinergic or sedative

properties and most frequently evaluated in studies which investigate DBI [12]. Following consent, hospitalisation and mortality data were obtained annually until death; this information was recorded by matching the National Health Index number with hospitalisations data from the New Zealand Ministry of Health [15]. Falls data were recorded at each interview by self-report (yes/no response).

Cognitive function was measured by the Modified Mini-Mental State Examination (3MS) [25]; functional status was measured using the Nottingham Extended Activities of Daily Living (NEADL) scale [26], an index scale measuring instrumental activities of daily living (IADLs); higher scores correspond to greater independence.

2.4 Statistical analysis

Data were analysed using Statistical Package for the Social Sciences Version 21®. Descriptive statistics provided an overview of the study cohort. DBI, cognitive function and functional status were analysed as continuous variables; hospitalisation and falls were analysed as nominal variables. Regression analyses were used to determine the association between DBI (at baseline) and outcomes (at 12-months', 24-months' and 36-months' follow-up), respectively. This association was determined using negative binomial regression (for hospitalisations and falls), Cox regression (for mortality) and linear regression (for cognitive function and functional status). Associations for hospitalisations and falls were measured by Relative Risk (RR), mortality by hazard ratios (HRs), cognitive function by differences in mean 3MS scores and functional status by differences in mean NEADL scores, along with the corresponding 95% confidence intervals (CIs) (significance $p<0.05$). Regression models were adjusted for baseline age (Māori only), gender, GP visits, socioeconomic deprivation, number of medicines prescribed and (depending on the outcome investigated) one of the following: all-cause hospitalisation, history of any falls, cognitive function (3MS) or functional status (NEADL). Cohorts were analysed separately as prevalence of DBI and risk factors profiles differed between ethnic groups.

3.0 Results

3.1 Demographic overview of the cohort

Table 1 provides a demographic overview of each cohort and reports the number of individuals prescribed ≥1 medications with a DBI>0 as well as the total DBI (mean ±SD) at each time-point. The mean number of medicines prescribed at each time-point was similar for both Māori and non-Māori. In total, there were 287, 223 and 198 medications with a DBI>0 prescribed at baseline, 12-months and 24-months, respectively.

At baseline and 12-months, the mean DBI was significantly higher ($p<0.01$) in the non-Māori cohort (0.28 ±0.5 and 0.27 ±0.5, respectively) compared to the Māori cohort (0.16 ±0.3 and 0.18± 0.5, respectively). At each time-point, Māori were significantly more likely to live in areas of increased deprivation ($p<0.01$). The mean 3MS score (at baseline, 12-months and 24-months) was significantly lower in the Māori cohort, than the corresponding mean 3MS score in the non-Māori cohort; and the functional status was similar for both the Māori and non-Māori cohorts; see Table 1.

Table 1 Demographic overview and exposure to medications with a Drug Burden Index (DBI)>0 for all individuals enrolled in LiLACS NZ at each time point

3.2 Prescribed medication that contributed to participants' Drug Burden Index (DBI)

At baseline, the most commonly prescribed medicines with a DBI>0 were zopiclone (4.8%) and doxazosin (4.8%), followed by amitriptyline (4.0%) and codeine (3.6%). See supplementary file for an alphabetical list of the medications with a DBI>0 prescribed for individuals enrolled in LiLACS NZ.

3.3 Drug Burden Index (DBI) and health-related outcomes

Table 2 provides an overview of the association between DBI at baseline and hospitalisations, falls, mortality, cognitive function and functional status, for all Māori individuals enrolled in LiLACS NZ at each time-point. A higher DBI was significantly associated with a greater risk of mortality (at 36-months' follow-up), adjusted HR (95% CIs) 1.89 (1.11, 3.20) p=0.02; see Table 2.

Table 2 The association between a higher Drug Burden Index (DBI) at baseline and outcomes at 12, 24 and 36-month follow-ups for all Māori individuals

Table 3 provides an overview of the association between DBI at baseline and hospitalisations, falls, mortality, cognitive function and functional status, for all non-Māori individuals enrolled in LiLACS NZ at each time-point. A higher DBI was significantly associated with a greater risk of mortality (at 12-months' follow-up), adjusted HR (95% CIs) 2.26 (1.09, 4.70) p=0.03 and impaired cognitive function (at 24-months' follow-up), adjusted mean difference in NEADL score (95% CIs) 0.89 (-3.89, -0.41) p=0.02; see Table 3.

Table 3 The association between a higher Drug Burden Index (DBI) at baseline and outcomes at 12, 24 and 36-month follow-ups for all non-Māori individuals

4.0 Discussion

Using data from LiLACS NZ, this paper reported the prevalence of exposure to medications with a DBI>0 in Māori (aged ≥80 years) and non-Māori (≥85 years) individuals living in New Zealand. For those individuals exposed to these medications, a DBI was calculated and the association between DBI and health-related outcomes was assessed. In Māori, a higher DBI was significantly associated with a greater risk of mortality (at 36-months' follow-up). In non-Māori, a higher DBI was significantly associated a greater risk of mortality (at 12-months' follow-up) and impaired cognitive function (at 24-months' follow-up). Overall, the proportion of individuals prescribed ≥1 medication with a DBI>0 increased from 31% at baseline, to 34% at 24-months. These figures are similar to previous studies conducted in community-dwelling older adults in Finland, Australia and the US [11], [27]–[29]. Like other studies which have investigated anticholinergic and sedative medication burden [28]–[30],

the most commonly prescribed drug classes, which contributed to an individual's DBI, were zopiclone, doxazosin, amitriptyline and codeine.

Māori were more likely to live in areas of greatest deprivation (NZdep score 8-10) and thus may be predisposed to an imbalance of socioeconomic resources such as income, education and occupation, which negatively impacts upon their health outcomes [31]. Although not investigated in this study, the association between increased deprivation and reduced cognitive function has been investigated in the literature [32]. Overall, the mean number of medicines prescribed in this study was lower than other studies. Moreover, the overall prevalence of medications with a DBI>0 prescribed in this cohort was approximately 33%, which is similar to previous studies [3], [33]–[36]. It may be the case that prescribers are more conservative when considering pharmaceutical therapy in octogenarians.

The lack of association between DBI and hospitalisations reported in this paper does not reflect the research literature [13]. For example, in a study of community-dwelling older adults (mean age 81 years) living in Finland, DBI was significantly associated with a greater prevalence of hospitalisation [27]. The lack of association between DBI and hospitalisations (in Māori) may be a result of Māoris' reduced engagement with western medicines [37]. Māori individuals have a more holistic approach to healthcare and many believe that the absence of 'taha wairua' (spiritual dimension) is a major weakness in modern healthcare services; this may influence their use of conventional healthcare and may affect the results reported in this study [38]. For non-Māori, the lack of association between DBI and hospitalisations may reflect that other factors have a greater impact on risk of hospitalisation.

Falls counts were self-reported in the LiLACS NZ study as the cohort was predominantly community-dwelling. The findings reported in this paper (i.e. there was no significant association between DBI and a greater risk of falls) could be due to under-reporting of falls, and are contrary to those of Wilson et al. who reported a significant association between DBI and a greater frequency of falls for individuals living in residential aged care facilities [3]. Wilson et al. observed a much higher prevalence of medications with a DBI>0 prescribed in the study cohort (>60%) compared to the prevalence reported in the LiLACS NZ study (approximately 33%) and, due to the setting of the Wilson study, it may have been more feasible to count the number of falls that occurred in study participants [3].

Mortality within these cohorts was low compared to those in residential care, and DBI was significantly associated with a greater risk of mortality (in Māori) at 36-months' follow-up only and (in non-Māori) at 12-months' follow-up only. This may have been the result of prescribed medications with a DBI>0, or unmeasured confounders associated with both medication use and mortality. The association was independent of a marker of health status (number of GP visits) and has been reported in a number of other studies, but has not been found in Māori [33], [39].

DBI was associated with reduced cognitivie function in non-Māori at 24-months' follow-up only; no association was found in Māori individuals. Due to the intense nature of data collection, some participants opted for a shorter version of the interview and thus cognitive function was not investigated for all individuals enrolled in LiLACS NZ at each time-point, this could have lead to a Type II error. According to previous studies, the association between DBI and cognitive function has been inconclusive. For example, using the anticholinergic component

of the DBI (DB_{AC}), Bostock et al. found no association with cognitive impairment [1]. Conversely, Best et al. and Kashyap et al. observed that DBI was associated with a greater risk of hospitalisation for delirium [34] and a decline in memory function [40], respectively. It should be noted that the Best et al. study was based in the hospital setting and reported a higher prevalence of medications with anticholinergic or sedative properties (50%) [34] than that observed in this cohort, and the prevalence of cognitive impairment reported by Kashyap et al. was as high at 86% [40].

As with cognitive function, an assessment of functional status was not completed for all individuals enrolled in LiLACS NZ at each time-point. Unlike cognitive function, a much larger proportion of the cohort was classed as functionally impaired at baseline and at subsequent follow-ups. In this study, a significant association between DBI and functional impairment was not observed at any time-point. Previous research investigating DBI and physical function has reported a significant association between DBI and functional status. However, previous studies were different in terms of the characteristics of the study population (i.e. size of the cohort, mean age, sex and setting within which the study took place) [29], [30], the prevalence of medications with a DBI>0 observed [30], [41] and the tools used to measure physical function [28]–[30], [41].

A key strength of this study is the data source. LiLACS NZ data collection was rigorous and undertaken by experienced 'ageing researchers' through a composite of elements (face-to-face interview, health assessment and analysis of GP records) [15]. This has resulted in a rich dataset and has permitted this longitudinal analysis of exposure to medications with a DBI>0. Moreover, medication data were collected from medicine bottles in participants' homes and adherence was confirmed by self-report. Although difficulties of engaging people in research, particularly ethnic minority groups, is widely acknowledged [42], LiLACS NZ investigators successfully engaged with Māori populations. This was advantageous as it resulted in a study population reflective of the older population of New Zealand [19]. However, it should be noted that prescribing practices have been shown to differ between different District Health Boards (DHBs) within New Zealand and globally between different countries [43], which limits the generalisability of the results. For example, West Coast DHB prescribed antipsychotics at more than double the rate of Manukau DHB in 2015 [44]. Differences in prescribing may be due to differences in drug reimbursement and local/national formularies. Despite this, these results serve as an important comparator for other longitudinal studies of DBI. The majority of previous studies of DBI have either been cross-sectional [11], [28], [29], [45]–[47], or had a much shorter follow-up period [1], [2], [4], [5], [34], [48], [49]. In this current study, DBI and outcomes were measured at three time-points. The attrition rate between the three time-points was comparable to other longitudinal studies of ageing (approximately 17%), and is an inevitable limitation of ageing research, i.e. attrition rates are higher than those studies of younger populations. Other than death, reasons for attrition may be due to lower levels of education, decreased health literacy and non-fluent in English [50]. Another strength of the study is that a total of five outcomes were assessed and outcomes data (hospitalisations and mortality) were taken from national registers, which also provided information on the indication for the hospitalisation. Although this study reports a significant association between medications with a DBI>0 and a greater risk of mortality and impaired cognitive function, this does not infer causality due to the effect of residual confounding [51]. For example, the analysis did not adjust for the number of comorbidities; those with a greater number of comorbidities are more likely to have a higher DBI.

The DBI itself has many strengths and limitations. The DBI is based on the evidence that anticholinergic medications inhibit muscarinic receptors in the central and peripheral nervous system [11]. The DBI has been utilised internationally in a number of studies across community, hospital and nursing home settings [12], and exposure to medications with a DBI>0 has been associated with a number of clinical outcomes such as cognitive impairment, functional impairment, more frequent falls, hospital-related falls and mortality [12]. Calculation of the DBI incorporates daily drug dose and the principles of dose response. However, the pharmacological equation used to calculate DBI does not account for patient-specific characteristics which may affect drug absorption and metabolism e.g. age, sex, food, comorbidities etc. Older people have an increased blood-brain-barrier permeability, and therefore exhibit altered pharmacokinetics and pharmacodynamics [9]. Consequently, MDD values approved by the New Zealand MIMS may not be a reliable indication of DR_{50} in this population group. Moreover, total DBI is calculated through the summation of the DBI associated with each medication, based on the assumption that cumulative DBI from multiple medications is a linear process. However, this assumption may be inaccurate, due to the synergistic interactions that occur between medications in the body [52]. The DBI it suitable for international use, through the substitution of approved MDD values, specific to the country in which it is being utilised. However, it is important to note that MDD values, approved in New Zealand, may not be comparable worldwide.

5.0 Conclusions

In this study, a higher DBI was significantly associated with mortality (in Māori and non-Māori) and impaired cognitive function (in non-Māori), when adjusted for confounding factors. Given demographic shifts, and the inconclusive results surrounding exposure to medications with a DBI>0 and their effect on health-related outcomes, future research should endeavour to investigate this relationship further. Nevertheless, strategies to manage the prescribing of medications with anticholinergic and/or sedative properties (e.g. medication reviews, deprescribing initiatives, educational interventions) should be employed in clinical practice. Pharmacists across all sectors, but particularly in hospital and general practice, are appropriately skilled to undertake such strategies.

Compliance with Ethical Standards

KC, NK, CR, RT, SM, OM, AR, JB and CH declare that they have no conflict of interest. This current analysis was supported by the Department for Employment and Learning (DEL), Northern Ireland, through a postgraduate studentship to KC. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Table 1 Demographic overview and exposure to medications with a Drug Burden Index (DBI)>0 for all individuals enrolled in LiLACS NZ at each time point

	Baseline (n=671)			12-months (n=510)			24-months (n=403)		
	Māori (n=267)	**Non-Māori (n=404)**	**P value**	**Māori (n=178)**	**Non-Māori (n=332)**	**P value**	**Māori (n=122)**	**Non-Māori (n=281)**	**P value**
Age (years, mean ±SD)	82.27 ±2.64	84.56 ±0.53	**<0.01**[*]	83.16 ±2.60	85.52 ±0.51	**<0.01**[*]	84.22 ±2.58	86.54 ±0.51	**<0.01**[*]
Female n (%)	160 (59.9)	214 (53.0)	0.50[†]	107 (60.1)	177 (53.3)	0.14[†]	78 (63.9)	146 (52.0)	**0.03**[†]
Number of all medicines prescribed (mean ±SD)	4.63 ±3.24	4.92 ±3.18	0.25[*]	5.38 ±3.57	5.29 ±3.33	0.78[*]	5.69 ±3.53	5.56 ±3.34	0.68[*]
Number of medications with DBI>0 n	77	210	**<0.01**[†]	58	165	**<0.01**[†]	54	144	0.83[†]
Total DBI (mean ±SD)	0.16 ±0.3	0.28 ±0.5	**<0.01**[*]	0.18 ±0.4	0.27 ±0.5	**0.01**[*]	0.22 ±0.4	0.28 ±0.5	0.26[*]
Individuals exposed to ≥1 medications with DBI>0 n (%)	63 (24.6)	146 (36.1)	**<0.01**[†]	38 (21.4)	117 (35.2)	**<0.01**[†]	38 (31.2)	100 (35.6)	0.39[†]
Socioeconomic deprivation (NZDep) n (%)									
0-4	37 (13.9)	101 (25.0)		27 (15.2)	83 (25.0)		16 (13.1)	71 (25.3)	
5-7	65 (24.3)	171 (42.3)		46 (25.8)	143 (43.1)		35 (28.7)	124 (44.1)	
8-10	165 (61.8)	132 (32.7)	**<0.01**[‡]	105 (59.0)	106 (31.3)	**<0.01**[‡]	71 (58.2)	86 (30.6)	**<0.01**[‡]
Cognitive function as per 3MS[¥] (mean ±SD)	89.7 ±15.8	91.0 ±10.6	**<0.01**[*]	89.4 ±10.6	92.4 ±8.4	**<0.01**[*]	89.9 ±10.0	92.2 ±9.8	**0.04**[*]
Functional status as per NEADL (mean ±SD)	17.2 ±4.6	17.6 ±4.0	0.25[*]	17.0 ±3.9	16.9 ±4.3	0.81[*]	17.3 ±3.6	16.6 ±4.1	0.11[*]

Key: DBI, Drug Burden Index; NZDep, New Zealand Deprivation Index score; 3MS, Modified Mini-Mental State Examination; [¥]Cognitive function was not assessed in all individuals; NEADL, Nottingham Extended Activities of Daily Living score; P values measure differences between Māori and non-Māori; [*]Two-samples t-test (significance $p<0.05$); [†]Chi-squared ($\chi 2$) test (significance $p<0.05$); [‡]Mann Whitney U test (significance $p<0.05$).

Table 2 The association between a higher Drug Burden Index (DBI) at baseline and outcomes at 12, 24 and 36-month follow-ups for all Māori individuals

	12-months' follow-up	24-months' follow-up	36-months' follow-up
Increased rate of hospitalisation RR (95% CI)† p value*	0.67 (0.32, 1.40) 0.28	1.31 (0.72, 2.39) 0.38	1.56 (0.79, 3.08) 0.20
Increased rate of falls RR (95% CI)† p value*	1.49 (0.76, 2.92) 0.25	1.32 (0.68, 2.57) 0.41	1.08 (0.53, 2.19) 0.83
Mortality HR (95% CI)‡ p value*	0.58 (0.11, 2.56) 0.51	0.87 (0.35, 2.18) 0.15	**1.89 (1.11, 3.20) 0.02**
Cognitive function Difference in mean 3MS score (95% CI)¥ p value*	1.88 (-5.35, 2.04) 0.38	2.24 (-2.69, 6.08) 0.45	2.38 (-3.62, 5.71) 0.66
Functional status Difference in mean NEADL score (95% CI)¥ p value*	0.49 (-0.82, 1.11) 0.77	0.55 (-1.36, 0.81) 0.62	1.01 (-1.99, 1.98) 1.00

Key: CI, Confidence interval; DBI, Drug burden index; NEADL, Nottingham extended activities of daily living; 3MS, Modified mini-mental state examination; RR, Relative Risk; HR, hazard ratio; †Negative binomial regression (significance p<0.05); ‡Cox regression (significance p<0.05); ¥Linear regression (significance p<0.05); *Adjusted for baseline age, gender, GP visits; socioeconomic deprivation, number of medicines prescribed and either prior all-cause hospitalisation, history of any falls, cognitive function or functional status (where applicable).

Table 3 The association between a higher Drug Burden Index (DBI) at baseline and outcomes at 12, 24 and 36-month follow-ups for all non-Māori individuals

	12-months' follow-up	24-months' follow-up	36-months' follow-up
Increased rate of hospitalisation RR (95% CI)† p value*	1.26 (0.87, 1.83) 0.22	1.15 (0.82, 1.61) 0.41	1.16 (0.81, 1.65) 0.43
Increased rate of falls RR (95% CI)† p value*	1.09 (0.76, 1.56) 0.65	1.06 (0.75, 1.51) 0.73	1.13 (0.80, 1.62) 0.49
Mortality HR (95% CI)‡ p value*	**2.26 (1.09, 4.70) 0.03**	1.52 (0.90, 2.55) 0.12	1.32 (0.91, 1.91) 0.14
Cognitive function Difference in mean 3MS score (95% CI)¥ p value*	0.04 (0.56, -1.57) 0.65	**0.89 (-3.89, -0.41) 0.02**	1.09 (-3.29, 0.97) 0.29
Functional status Difference in mean NEADL score (95% CI)¥ p value*	0.36 (-1.22, 0.20) 0.16	0.41 (-1.20, 0.39) 0.31	0.49 (-1.01, 0.89) 0.90

Key: CI, Confidence interval; DBI, Drug burden index; NEADL, Nottingham extended activities of daily living; 3MS, Modified mini-mental state examination; RR, Relative Risk; HR, hazard ratio; †Negative binomial regression (significance p<0.05); ‡Cox regression (significance p<0.05); ¥Linear regression (significance p<0.05); *Adjusted for baseline age, gender, GP visits; socioeconomic deprivation, number of medicines prescribed and either prior all-cause hospitalisation, history of any falls, cognitive function or functional status (where applicable).