Sedative load and frailty among community-dwelling population aged ≥65 years

Abstract

Objective: To explore the association between use of sedative drugs and frailty.

Design: Cross-sectional study.

Setting: First wave of The Irish Longitudinal Study on Ageing (TILDA), a nationally representative cohort of the community-dwelling population aged ≥50 years in Ireland.

Participants: 1,642 men and 1,804 women aged ≥65 years.

Measurements: Regular use of sedative drugs determined according to the sedative load model, frailty phenotype status and frailty deficit index (FI) score assessed using validated, established protocols.

***Results*:** Overall, 19% of the participants took sedative drugs, most frequently hypnotics and antidepressants. Sedative drug use was at 46% for frail, 23% for prefrail and 9% for non-frail participants. After adjustment for covariates, sedative load was positively associated with being prefrail (OR=1.27; 95% CI 1.11-1.46) and frail (OR=1.30; 95% CI 1.02-1.64). Advancing age but not sex remained significant ($p<0.001$). After adjustment for covariates, the association between sedative load and the frailty deficit index (FI) was also significant at $p\leq0.001$ (β =1.77; 95% CI 1.13-2.42).

Conclusion: Higher sedative load was positively associated with phenotype frailty and the frailty deficit index. This suggests that careful consideration must be given when prescribing sedatives to frail older adults, who are most vulnerable to adverse drug reactions and adverse health outcomes.

Running title: Sedative load and frailty in older adults

Key words: sedative load, frailty, drug utilisation, ageing, frailty index

INTRODUCTION

Older people are susceptible to adverse drug events owing to the diminishing physiological reserve associated with ageing.[1] This can be exacerbated further by acute or chronic diseases and by the drugs used to treat them.[2] Older populations are often prescribed a range of drugs with sedative properties (e.g. psychotropics).[3] Sedation is defined as subjective feelings of drowsiness and sleepiness, but also as decreased psychomotor functioning, which can be measured in objective tests.[4] Sedative drugs have been associated with falls, fractures, physical and cognitive impairment and disability among community-dwelling older people.[3,5,6,7]

With more drugs being taken concomitantly, the risk of interactions and cumulative sedative effects is increased[1,8,9], leading to the development of different models to study the sedative effect of drugs.[10] The "sedative load model" was developed to quantify the cumulative effect of taking multiple drugs with sedative properties.[11] Older age, female sex, lower education levels, impaired mobility depression and dementia are predictors of sedative load exposure. [3,8]

The global expansion of population ageing has lead to the clinical condition of frailty becoming an increasing challenge. Frailty develops as a consequence of age-related declines in many physiological systems, resulting in vulnerability to stressors (e.g. infection or hospitalisation) and adverse health outcomes.[12] Fried et al.[13] characterised frailty as a clinical phenotype of at least three of five indicators: unintentional weight loss, slow walking speed, self-reported exhaustion, low levels of activity and muscle weakness. Frail individuals are at increased risk of falls, hospitalisation, worsening mobility, disability and death.[12] Frailty has also been linked to impaired global cognition and cognitive decline.[14,15] Using a different approach, Rockwood et al.[16] have also characterised frailty, as an age-associated, non-specific accumulation of deficits resulting in vulnerability to stressors and adverse outcomes. They present this accumulation of deficits as an index score called the frailty deficit index (FI).

Frail older adults are more susceptible to age- and disease-related changes in their pharmacokinetic and pharmacodynamic responses to drugs.[2,17] This is compounded further as frail individuals are more likely to be administered several medications, resulting in polypharmacy..[17,18] In community-dwelling older people living in Finland, higher sedative load was associated with

poorer physical performance, balance and mobility.[19,20] In contrast, higher sedative load was not associated with poorer physical or cognitive performance, but was associated with impairments in activities of daily living (ADLs) and Instrumental ADLs (IADLs) among community-dwelling older men in Australia.[8] Data regarding the direct association of sedative load and frailty has not been published.

In this study we assessed the potential relationship between sedative load exposure (independent variable) and frailty (dependent variable) measured using the phenotype and deficit index definitions.

METHODS

Study population

Cross-sectional analyses were performed using data from the first wave of *The Irish Longitudinal Study on Ageing* (TILDA) conducted between 2010-2011. The TILDA study cohort includes 8,175 participants representative of the community-living population aged 50 and older living in Ireland. Households were selected in geographic clusters from a list of all Irish residential addresses. Each household was visited by an interviewer and any resident aged 50 or older as well as their spouse or partner was invited to participate. The household response rate was 62.0%. Ethical approval was obtained from the Trinity College Dublin Research Ethics Committee and all participants provided written informed consent. Those with cognitive impairment that prevented consent being given were not included in the study for ethical reasons. Participants were interviewed in their homes and answered questions on health, social interactions, and financial circumstances. Each participant was invited to travel to a health centre for a comprehensive health assessment. The sampling procedure, the home interview, and the health assessment have been described in detail previously.[21] From the total sample of 8,175 participants, 3,446 aged 65 and older provided details of their regular medication use (Tables 1 and 2). Of these, 1,718 participants attended the health centre assessment and provided sufficient data to assess their frailty status (Table 3).**Assessment of sedative load (SL) score**

The in-home inventory of drugs and food supplements was conducted by asking the question "*Now I would like to record all medications that you take on a regular basis, like every day or every week. This will include prescription and non-prescription medications, over-the-counter medicines, vitamins, and herbal and alternative medicines.*" No information about dose, frequency, quantity or prescription status was obtained.

Drugs were coded using the ATC (Anatomical-Therapeutic-Chemical) classification system[22] and the effect of taking multiple drugs with sedative properties was calculated using the sedative load model.[3,11] Drugs were categorized as: primary sedatives e.g. anxiolytics (Group 1); drugs with a sedating component or side effect e.g. selective serotonin reuptake inhibitors (Group 2); drugs with sedation as a potential adverse reaction e.g. acetylcholinesterase inhibitors (Group 3); all other medicines with no known sedative properties (Group 4). Drugs included in groups 1,2 and 3-4 were assigned sedative ratings of 2, 1 (Table 2) and 0 respectively. Sedative load was calculated as the sum of the sedative ratings at an individual level, for regularly used drugs. Sedative Load (SL) scores of 0, 1-2 and 3 indicated no, low and high sedative load respectively.

The sedative load model was first published in 2003 and was updated in 2011.[3,11] In our study, this model was assessed and modified to include drugs taken by participants in this study and to reflect the current knowledge about sedative effects of drugs. Two experienced clinical pharmacists (IM,JP) independently consulted, reviewed and amended scores for the original updated list of drugs[11] using standard and widely accepted reference sources e.g. product characteristics (SmPC) information, and Maudsley Prescribing Guidelines[23]. Relevant MEDLINE articles [24-26] informed the scoring of drugs not included on the list. Scores were reviewed by an experienced psychogeriatrician and disagreements were resolved by consensus. Drugs included in our analysis with respective scoring are listed in Table 2.

Frailty Measures

Phenotype frailty was operationalized using population-specific cut-points following the methodology of Fried and colleagues[13]. This was done owing to differences in the assessments of

weakness (sex- and bmi-adjusted grip-strength measured using baseline dynamometer), physical activity (sex-adjusted kilocalories (kcals) from the International Physical Activity Questionnaire-Short Form [IPAQ-SF]), and walking speed (sex- and height-adjusted cm/s using the GAITRite portable walkway) that made using the absolute cut-points reported by Fried and colleagues inappropriate. Weight loss was ascertained by the question "In the past year have you lost 10 pounds (4.5 kg) or more in weight when you were not trying to." Exhaustion was captured using two items from the 20-item Centre for Epidemiological Studies Depression (CES-D) scale. Participants were asked how often they felt that "I could not get going" and "I felt that everything I did was an effort". A response of "moderate amount/all of the time" to either question was considered as "exhaustion." The presence of 0, 1-2 and ≥3 of the five criteria classified participants as non-frail, prefrail (an intermediate state) and frail, respectively. The operationalization of the frailty phenotype in the TILDA cohort at Wave 1 has been described previously.[27,28]

Additionally, a frailty deficit index (FI) was constructed using 40 self-reported health deficits from the TILDA home interview followed previously published methodology (Appendix 1).[16,29] The 40 deficits were associated with poor health, had a prevalence of 5-80%, were distributed across several health domains and were associated with advancing age.[16] Each deficit was coded as present (1) or absent (0). The total was then summed and divided by 40. This produced index scores between 0.0 and 1.0. List of 40 deficits included in FI is in Appendix.

Demographic, Health and Lifestyle Measures

Demographics included age, sex, education (reference group: secondary/higher) and marital status. The health measures recorded were: self-rated health (Ecellent/Very good/Good/Fair/ Poor); disability (the inability to perform one or more Instrumental/Activities of Daily Living (IADL or ADL))[30,31]; falls (≥1 self-reported fall in the past year); the number of chronic diseases or conditions (recorded as self-reported physician's diagnosis of heart attack, heart failure, angina, hypertension, high cholesterol, stroke, diabetes, lung disease, asthma, arthritis and osteoporosis); the number of all medications taken regularly (excluding supplements); underweight (BMI <18.5); obese (BMI ≥30); self-reported difficulty sleeping; cognitive impairment

(MMSE - Mini mental state exam score ≤24)[32]; self-rated memory; depressive symptoms (CES-D - The Center for Epidemiologic Studies Depression Scale score ≥16)[33]; anxiety (HADS-A - Hospital Anxiety and Depression Scale – Anxiety score ≥11) and loneliness. Life-style factors included alcohol consumption (defined as a yes/no response to the question "Do you drink alcohol?") and smoking status (defined as current/ past/never based on two questions "Have you ever smoked cigarettes, cigars, cigarillos or a pipe daily for a period of at least one year?" and "Do you smoke at the present time?").

Statistical analyses

Demographic, health and lifestyle measures were presented as means and standard deviations or counts and percentages. Comparisons across different SL and frailty groups were conducted using chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables including SL score and FI score.

Multinomial logistic regression analyses, adjusted for demographic, health and lifestyle factors, estimated odds ratios (OR) and 95% confidence interval (CI) for the association between SL score and the phenotype frailty, allowing the modelling of the prefrail and frail states (reference group: non-frail).

Multivariate linear regression was used to determine associations between the SL and FI scores. Unstandardized regression coefficients (B) with 95% CI were measured with accompanying p-values. Analyses were adjusted for the same covariates listed above. Analyses were performed using SPSS 18 (SPSS for Windows Release 18.0).

RESULTS

Characteristics of the study population and sedative load (SL)

Mean (SD) age was 73.0 (±6.4) years, ranging from 65 to 99 years and 52.4% were female. Of the 3,446 participants, 2,900 (84.2%) reported taking at least one regular drug. Mean (SD) number of reported drugs was 3.3 (±2.7; range 0 to 16) per participant. Sedative drugs were used

by 668 (19.4%) participants. Mean (SD) sedative load was 0.41 (±1.00; range 0 to 9). Sedative load was higher in women (0.50 [±1.09], p≤0.001), than in men (0.32 [±0.88]) and highest in the 75-84 years group (0.51 ±1.11) compared to those aged 65-74 years (0.36 ±0.93) or ≥85 years, (0.48 ±0.97) respectively; p≤0.001. Detailed characteristics of this cohort by SL are provided in Table 1.

The most frequently used primary sedatives (Group 1) were hypnotics (ATC N05C), and drugs most used with sedation as a prominent side effect (Group 2) were SSRIs (ATC N06AB) within antidepressants. Cohort SL score was 1,421. Hypnotics (ATC N05C) were the major contributor with an overall SL score of 450 ahead of antidepressants (ATC N06) with an overall SL score of 350. Details of sedative drug use are provided in Table 2.

Prevalence of frailty

Of the 3,446 participants, 1,718 attended the health centre assessment and provided sufficient data to assess their frailty status. The prevalence of frailty in this sample was 4.2% (n=72), 39.1% (n=672) were prefrail and 56.7% (n=974) were non-frail. Frail participants were significantly older, had more chronic diseases, poorer education and more I/ADL disability. They had significantly higher drug use, polypharmacy (5≥ drugs) and sedative drugs use. Prefrail participants were an intermediate group performing significantly worse on these measures compared with the non-frail group but significantly better than the frail group. Sedative drug use was at 46% for frail, 23% for prefrail and 9% for non-frail participants. More women were prefrail or frail, but not significantly so. Mean FI score increased with frailty status through all three categories (Table 3 and Figure 1).

The relationship between frailty and sedative load (SL)

Mean SL was independently associated with frailty using both the frailty phenotype and FI models as shown in (Figure 1. In unadjusted analyses, frail (OR 2.08, 95%CI 1.70-2.54) and prefrail (OR 1.63, 95%CI 1.43-1.86) participants were significantly more likely to use medicines with sedative properties than non-frail participants. After adjustment for all listed variables in Table 1, frailty (OR 1.30, 95%CI 1.02-1.64; p=0.023) and prefrailty (OR 1.27, 95%CI 1.11-1.46; p<0.001))

196 remained significantly associated with SL score.

197 Multiple regression analysis was used to independently test if the SL was significantly
198 correlated with FI score. In unadjusted analyses higher FI scores were associated with higher SL
199 cores (β=0.30; p<0.001. B=2.54; 95% CI 2.15-2.92). The adjusted model for all covariates listed in
200 Table 1, explained 10.4% of the variance (R^2=0.104, F(10.72)=124.64, p≤0.001) and the association
201 between SL and the FI score was significant at p≤0.001 (B=1.77; 95% CI 1.13-2.42).

202 Respondents who did not provide data on frailty status (*n* = 1,728) were more likely to be
203 older, less educated, took more medicines and had a higher SL at p<0.05. There was no difference
204 in sex or number of comorbidites reported between both groups.

205

206 **DISCUSSION**

207 This was the first study to investigate the association between SL and frailty in community-
208 dwelling adults aged 65+ years. Our data indicates the use of sedative drugs was positively
209 associated with being both prefrail and frail in unadjusted and adjusted analyses using two
210 established methodologies to assess frailty, phenotype frailty and the FI.

211 Our findings revealed that one in five participants in our study took at least one sedative
212 drug, which falls between the Australian and Finnish studies where 15 % and 29% of participants
213 reported sedative drug use, respectively.[3,8] These differences may emerge from age/sex
214 characteristics of the populations studied, their cultural background, environmental differences
215 and doctors' prescribing habits. Those who reported higher SL in our study had poorer health in
216 line with previous studies. [3,8] The drugs which contributed most to SL in our study were hypnotics
217 (Group 1) and SSRIs with other antidepressants (Group 2). This is similar to the Finnish study[3] but
218 differs from the Australian study[8], where anxiolytics (Group 1) and antidepressants (Group 2)
219 were the major contributors to overall SL. We updated the original Finnish model to reflect current
220 knowledge regarding the sedative effect, as available from standard reference sources. The
221 majority of changes involved re-scoring between Groups 1 to 2, and only lithium moved between
222 the categories of SL and no SL. We believe the modified model better reflects the sedative burden

of reported drugs and both the original and modified models of SL were significantly associated with frailty (Appendices 1 and 2).

Frail participants in our cohort were older and had poorer health indicators, characteristic of frailty in other studies.[12,13] Moreover, the respective exposure of frail and prefrail participants to sedative drugs was five and three times higher compared to their non-frail counterparts. Adjusting for relevant confounders, SL was significantly associated with both frailty and prefrailty. For each increase in SL score, the likelihood of being frail or prefrail increased by 30% and 27%, respectively. While a clear age gradient existed, there was no sex difference detected in our sample despite reports that females are more likely to be frail..[13,34] SL was also significantly associated with higher FI score.

Loss of muscle mass and function (sarcopenia) is a marker of frailty and may be influencing the association between SL and frailty. Similarly, it is known that a decrease in lower limb muscle mass, strength and function leads to poorer gait and mobility.[35] Thus, the association between SL and frailty may be explained by the adverse impact of sedative exposure on physical function, superimposed on a sarcopenia-related frailty process. These findings could have important clinical implications with respect to prevention of other adverse health outcomes such as falls, fractures and disability. These adverse outcomes are common among older adults, result from both sedative drug use and frailty and constitute a significant burden to healthcare systems worldwide. [12,13,36,37] This suggests that minimising sedative exposure in prefrail and frail older adults may be clinically significant given their increased vulnerability to adverse drug reactions and adverse health outcomes. Longitudinal and intervention studies with measures of sarcopenia, frailty and SL may help to better inform these relationships. Indeed additional future waves of the TILDA study will contribute to our understanding of the impact of increasing sedative load exposure among the prefrail and frail.

Polypharmacy, high-risk treatment regimens and the Drug Burden Index (an alternate tool to the SL model) were previously associated with frailty at baseline and incident frailty after 2-years. [18,38] However, the strengths of our study included the use of a large sample, that was very well characterised using a broad range of epidemiologically and clinically validated measures. Also,

the association between SL and frailty was confirmed using two independent and methodologically different measures of capturing frailty, lending additional support to the relationship between SL and frailty. Furthermore, medication data was collected by trained interviewers in the home reducing self-report recall bias.[39]. Few methods exist to measure the burden of sedative drugs but the advantages of the SL model are three-fold: It includes drugs with sedative properties prescribed for somatic diseases, it describes cumulative exposure to drugs exerting sedative effects through multiple mechanisms in the CNS, and it incorporates a sedative rating for each drug. [3,8,19,20,]

There were some limitations of the study. The SL model has not been validated against *in vitro* or *in vivo* measures of sedative activity, or objective tests of altered psychomotor functioning. Drug dosage and frequency were not recorded. Only regularly taken drugs were included, not those taken 'when required' (prn). There may also be some limitation in terms of generalising findings in relation to the SL model, due to variations in the prescribing patterns of different countries and healthcare systems. To provide wider generalizability of these study findings, similar research using the same sedative load protocol should be replicated in different population. The necessity to collect objective measurements of grip strength and walking speed in order to measure the frailty phenotype status is also a potential limitation. While objective measures are considered more reliable than self-report measures, they are often less feasible, particularly in a clinical setting. Indeed participants in this study who did not perform a health assessment, could not be assessed for frailty, although they were older, took more drugs, and had a higher SL. Similarly, individuals with cognitive impairment that prevented informed consent, and are likely to be frail, were also excluded from this study. This suggests that our estimation of the association between sedatives and frailty may be conservative. Finally, cross-sectional data do not allow assessment of the causality of the relationship between frailty and SL. Some of these limitations will be overcome during subsequent waves of this longitudinal study of ageing.

CONCLUSIONS

The use of drugs with sedative properties in older Irish adults is significant and more prevalent in the subpopulation with the poorest health status. In this study, two models of frailty

were associated with higher SL. As frail, and prefrail, people are more susceptible to adverse responses to drugs and adverse health outcomes, additional consideration when choosing appropriate sedative drugs is needed in this vulnerable group. However, further studies are needed to assess the impact over time of greater sedative use among prefrail and frail older adults.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Mr. Peklar and all co-authors take responsibility for the integrity of the data and the accuracy of the data analysis. Mr. Peklar: wrote manuscript, designed and performed research, analysed data. Dr. O'Halloran: wrote manuscript, performed research, analysed data. Dr. Maidment: designed research, analysed data Dr. Henman: designed and performed research. Professor Kenny: designed research. Dr. Kos: designed and performed research.

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Table 1. Participant Characteristics by Sedative Load Category (n=3,446)

		Total Population	Sedative Load [n(%)]			
		(n=3,446) [n(%)]	(n=2,778) **0**	(n=495) **1 or 2**	(n=173) **≥3**	P-value
Age (Yrs)	65-74	2,137 (62.0)	1,771 (82.9)	279 (13.1)	87 (4.1)	
	75-84	1,091 (31.7)	843 (77.3)	172 (15.8)	76 (7.0)	<0.001
	≥85	218 (6.3)	164 (75.2)	44 (20.2)	10 (4.6)	
Sex (Female)		1,804 (52.4)	1,387 (49.9)	310 (62.6)	107 (61.8)	<0.001
Education (None/primary)		1,514 (44.0)	1,175 (42.3)	255 (51.5)	84 (48.6)	<0.001
Married		2,034 (59.0)	1,708 (61.5)	245 (49.5)	81 (46.8)	<0.001
Alcohol users		1,822 (63.1)	1,516 (64.8)	228 (55.9)	78 (55.7)	0.001
Currently smoking		469 (13.6)	357 (12.9)	78 (15.8)	34 (19.7)	0.011
No. of chronic conditions (Mean, SD)		2.21 (1.54)	2.06 (1.46)	2.76 (1.64)	3.06 (1.87)	<0.001
Self rated health (Fair/Poor)		564 (16.4)	348 (12.5)	152 (30.8)	64 (37.0)	<0.001
No. of drugs (Mean, SD)		3.33 (2.71)	2.79 (2.39)	5.16 (2.60)	6.86 (3.04)	<0.001
IADL disability (≥1 disability)		170 (4.9)	121 (4.4)	37 (7.5)	12 (6.9)	<0.001
ADL disability (≥1 disability)		431 (12.5)	262 (9.4)	111 (22.4)	58 (33.5)	<0.001
Self rated memory (Fair/Poor)		705 (20.5)	487 (17.5)	153 (30.9)	65 (37.6)	<0.001
COPD/Asthma		440 (12.8)	319 (11.5)	85 (17.2)	36 (20.8)	<0.001
MCI/Dementia (MMSE score ≤24)		245 (10.5)	175 (9.2)	50 (15.5)	20 (15.7)	<0.001
CVD		1,993 (57.8)	1,559 (56.1)	319 (64.4)	115 (66.5)	<0.001
Arthritis		1,304 (37.8)	960 (34.6)	241 (48.7)	103 (59.5)	<0.001
Stroke		95 (2.8)	53 (1.9)	25 (5.1)	17 (9.8)	<0.001
Diabetes		365 (10.6)	276 (9.9)	68 (13.7)	21 (12.1)	0.032
Depression (CES-D score ≥16)		282 (8.4)	165 (6.0)	77 (16.0)	40 (24.1)	<0.001
Anxiety (HADS-A score ≥ 11)		245 (9.0)	157 (7.1)	57 (15.2)	31 (23.7)	<0.001
Chronic pain (Moderate/severe)		903 (26.2)	591 (21.3)	220 (44.5)	92 (53.2)	<0.001
Difficulty sleeping (Most of the time)		383 (11.1)	245 (8.8)	91 (18.4)	47 (27.2)	<0.001
Falls (≥1 in past year)		754 (21.9)	551 (19.8)	137 (27.7)	66 (38.2)	<0.001
Loneliness (moderate/most of the time)		285 (8.3)	190 (6.8)	62 (12.5)	33 (19.2)	<0.001

I/ADL – Instrumental/Activities of Daily Living.
COPD – Chronic Obstructive Pulmonary Disease.
MCI – Mild Cognitive Impairment.
MMSE – Mini Mental State Examination
CVD - Cardiovscular disease (high blood pressure, atrial fibrillation, transient ischemic attack).
CES-D – Center for Epidemiological Studies –Depression scale.
HADS-A – Hospital Anxiety and Depression Scale – Anxiety module.

436 **Table 2.** Categorisation of Drugs Contributing to Sedative Load in the Cohort (n=3,446)

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Group	ATC	INN Reported by Participants	N	%
Antidepressants	N06A	clomipramine#, trimipramine#, lofepramine#, amitriptyline#, dothiepin#,fluoxetine, citalopram, paroxetine, sertraline, escitalopram, trazodone#, mirtazapine#, venlafaxine, duloxetine	265	7.7%
Hypnotics	N05C	flurazepam#, nitrazepam#, flunitrazepam#, lormetazepam#, temazepam#, zopiclon#, zolpidem#, zaleplon#	223	6.5%
Opioid analgesics	N02A	morphine, oxycodone, dihydrocodeine, codeine (also combinations), fentanyl, dextropropoxyphene, buprenorphine, tramadol (also combinations), meptazinol	133	3.9%
Antiepileptics	N03	phenobarbital#, primidone, phenytoin, clonazepam#, carbamazepine, valproic acid, tiagabine, lamotrigine, gabapentin#, levetiracetam, pregabalin#	125	3.6%
Anxiolytics	N05B	diazepam#, chlordiazepoxide#, lorazepam#, bromazepam#, clobazam#, prazepam#, alprazolam#	88	2.6%
Antipsychotics (both conventional&atypical)	N05A	chlorpromazine#, prochlorperazine#, sulpiride, olanzapine#, quetiapine#, risperidone	42	1.2%
Propulsives	A03FA	Domperidone	21	0.6%
Anti-Parkinson Drugs	N04	biperiden, ropinirole, pramipexole, rotigotine	12	0.3%
Muscle relaxants	M03BX	baclofen, tizanidine	6	0.2%
Other		clonidine, cinnarizine, zolmitriptan, valerian extract#	8	0.2%
Opioid antitussives	R05DA	codeine, dextromethorphan, dihydrocodeine	4	0.1%
Antihistamine	R06	chlorphenamine, promethazine#	3	0.1%
No of respondents reporting at least one drug with SL≥1			668	19.4%

Drug is included in "group 1" (SL score 2)

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Table 3. Modified Sedative load, and participant characteristics, by frailty phenotype status (n=1,718)

Independent Variables	Frailty Phenotype Status		
	Robust 974 (56.7)	**Prefrail** 672 (39.1)	**Frail** 72 (4.2)
Frailty Index (FI) score (Mean, SD)	**0.11 (0.08)**	**0.18 (0.11)****	**0.32 (0.12)****
Exposure to sedative drugs (SL ≥1)	**84 (8.6)**	**153 (22.8)****	**33 (45.8)****
Sedative load score (Mean, SD)	**0.17 (0.65)**	**0.50 (1.05)****	**0.89 (1.22)****
Age (Mean, SD)	70.12 (4.44)	72.45 (5.56)**	76.17 (6.59)**
Sex (Female)	476 (48.9)	361 (53.7)	40 (55.6)
Education (none/primary)	291 (29.9)	237 (35.3)*	30 (41.7)*
Married	719 (73.8)	438 (65.2)**	39 (54.2)**
Rx medication exposure	766 (78.6)	584 (86.9)**	71 (98.6)**
No. of drugs (Mean, SD)	2.53 (2.28)	3.69 (2.74)**	5.46 (2.89)**
No. of chronic diseases (Mean, SD)	1.93 (1.37)	2.39 (1.57)**	3.60 (1.67)**
Polypharmacy (≥5 of drugs)	176 (18.1)	236 (35.1)**	39 (54.2)**
IADL disability **(≥1)**	13 (1.3)	26 (3.9)**	10 (13.9)**
ADL disability **(≥1)**	45 (4.6)	89 (13.2)**	29 (40.3)**
Global Cognitive Function (Mean MMSE score, SD)	28.41 (1.77)	28.00 (2.17)**	27.08 (2.66)**
Depression (CES-D ≥ 16)	26 (2.7)	62 (9.5) **	21 (29.6) **
Anxiety (HADS A ≥ 11)	50 (5.5)	66 (10.9) **	10 (17.2) **

I/ADL – Instrumental/Activities of Daily Living.
MMSE – Mini-Mental State Examination.
CES-D – Center for Epidemiological Studies –Depression scale.
HADS-A – Hospital Anxiety and Depression Scale –Anxiety schedule.
*p<0.05, **p<0.001

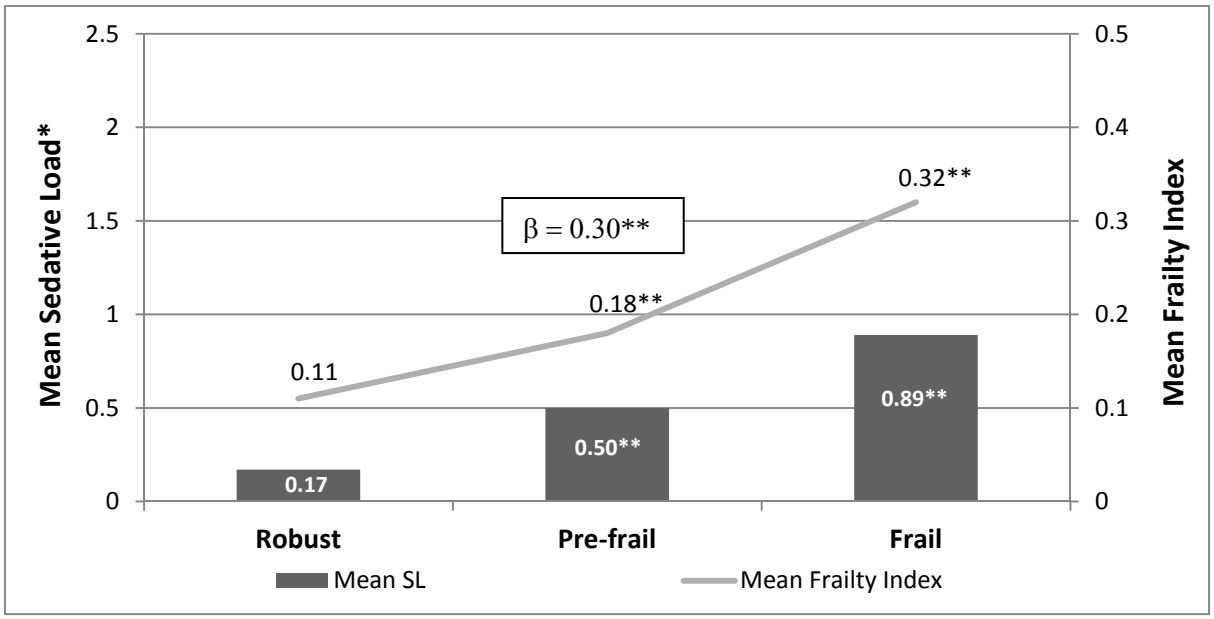

Figure 1. Unadjusted mean sedative load (SL) score was associated with prefrailty, frailty and frailty index score (FI) among participants aged 65+ years (n=1,718).
**p<0.001

Appendix I. Adjusted model of association between the **modified** sedative load (SL) score and frailty phenotype status (n=1,718).

Variable	Category	Prefrail		Frail	
		Adjusted OR [95% CI]	p-value	Adjusted OR [95% CI]	p-value
Sedative load (SL) score	[continuous variable]	1.31 (1.14-1.51)	≤0.001	1.43 (1.08-1.90)	0.014
Age (years)	[continuous variable]	1.10 (1.08-1.13)	≤0.001	1.29 (1.21-1.37)	≤0.001
Depression	[continuous variable]	1.08 (1.05-1.10)	≤0.001	1.17 (1.11-1.24)	≤0.001
Cognitive impairment	[continuous variable]	0.90 (0.84-0.96)	≤0.001	0.85 (0.74-0.97)	0.020
Sex	Male	1		1	
	Female	1.16 (0.91-1.49)	0.229	0.96 (0.49-1.86)	0.901
Education	Secondary or higher	1		1	
	None/Primary	0.84 (0.65-1.08)	0.173	0.63 (0.31-1.27)	0.197
CVD	No	1		1	
	Yes	1.07 (0.85-1.35)	0.577	1.67 (0.77-3.60)	0.192
Stroke	No	1		1	
	Yes	2.83 (1.16-6.88)	0.022	7.22 (1.89-27.58)	0.004
Diabetes	No	1		1	
	Yes	2.07 (1.38-3.11)	≤0.001	1.95 (0.77-4.95)	0.159
Arthritis	No	1		1	
	Yes	1.20 (0.94-1.53)	0.150	2.05 (1.04-4.03)	0.037
COPD/asthma	No	1		1	
	Yes	0.94 (0.67-1.34)	0.749	1.32 (0.60-2.91)	0.490
Smoking	Never	1		1	
	Current smoker	1.45 (0.96-2.19)	0.076	3.84 (1.40-10.55)	0.009
	Past smoker	1.09 (0.85-1.40)	0.506	1.32 (0.63-2.76)	0.464
Alcohol consumption	No	1		1	
	Yes	0.77 (0.60-0.99)	0.044	0.82 (0.41-1.64)	0.576
BMI<18.5 and >30)	No	1		1	
	Yes	1.32 (1.03-1.69)	0.029	1.40 (0.70-2.82)	0.344
Disability ADL	None	1		1	
	≥1 ADL	2.23 (1.44-3.46)	≤0.001	4.14 (1.86-9.21)	≤0.001
	≥1 IADL	2.15 (0.99-4.64)	0.052	7.07 (2.12-23.55)	0.001
Self-rated health	Excellent/Very good/Good	1		1	
	Fair/Poor	2.54 (1.63-3.94)	≤0.001	11.90 (5.52-25.66)	≤0.001
Loneliness	None of the time	1		1	
	Most of all of the time	0.86 (0.50-1.47)	0.578	0.79 (0.28-2.21)	0.658

Appendix 2. Adjusted model of association between the **original** sedative load (SL) score and frailty phenotype status (n=1,718).

Variable	Category	Prefrail		Frail	
		Adjusted OR [95% CI]	p-value	Adjusted OR [95% CI]	p-value
Sedative load score	[continuous variable]	1.35 (1.16-1.56)	≤0.001	1.49 (1.10-2.01)	0,010
Age (years)	[continuous variable]	1.10 (1.08-1.13)	≤0.001	1.29 (1.21-1.37)	≤0.001
Depression	[continuous variable]	1.08 (1.05-1.10)	≤0.001	1.17 (1.11-1.23)	≤0.001
Cognitive impairment	[continuous variable]	0.90 (0.84-0.96)	≤0.001	0.85 (0.74-0.98)	0,021
Sex	Male	1		1	
	Female	1.16 (0.91-1.48)	0,242	0.96 (0.49-1.86)	0,891
Education	Secondary or higher	1		1	
	None/Primary	0.84 (0.65-1.09)	0,181	0.63 (0.31-1.28)	0,202
CVD	No	1		1	
	Yes	1.07 (0.85-1.36)	0,558	1.68 (0.78-3.62)	0,188
Stroke	No	1		1	
	Yes	2.83 (1.16-6.89)	0,022	7.20 (1.88-27.54)	0,004
Diabetes	No	1		1	
	Yes	2.09 (1.39-3.14)	≤0.001	1.98 (0.78-5.01)	0,152
Arthritis	No	1		1	
	Yes	1.20 (0.94-1.54)	0,138	2.06 (1.05-4.05)	0,035
COPD/asthma	No	1		1	
	Yes	0.95 (0.67-1.35)	0,770	1.34 (0.61-2.94)	0,474
Smoking	Never	1		1	
	Current smoker	1.45 (0.96-2.18)	0,079	3.81 (1.39-10.45)	0,010
	Past smoker	1.09 (0.84-1.39)	0,524	1.30 (0.62-2.73)	0,486
Alcohol consumption	No	1		1	
	Yes	0.78 (0.60-1.00)	0,051	0.83 (0.42-1.66)	0,602
BMI<18.5 and >30)	No	1		1	
	Yes	1.32 (1.03-1.69)	0,027	1.41 (0.70-2.84)	0,334
Disability ADL	None	1		1	
	≥1 ADL	2.21 (1.43-3.44)	≤0.001	4.10 (1.84-9.12)	≤0.001
	≥1 IADL	2.16 (1.00-4.67)	0,050	7.08 (2.12-23.62)	≤0.001
Self-rated health	Excellent\Very good\Good	1		1	
	Fair\Poor	2.53 (1.63-3.93)	≤0.001	11.88 (5.51-25.62)	≤0.001
Loneliness	None of the time	1		1	
	All or most of the time	0.87 (0.51-1.50)	0,624	0.81 (0.29-2.26)	0,690