

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 $p \leq 0.001$ ($\beta = 1.77$; 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

31 INTRODUCTION

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

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

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

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

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

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

67

68 **METHODS**

69 **Study population**

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

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

91 Drugs were coded using the ATC (Anatomical-Therapeutic-Chemical) classification
92 system²² and the effect of taking multiple drugs with sedative properties was calculated using the
93 sedative load model.^{3,11} Drugs were categorized as: primary sedatives e.g. anxiolytics (Group 1);
94 drugs with a sedating component or side effect e.g. selective serotonin reuptake inhibitors (Group
95 2); drugs with sedation as a potential adverse reaction e.g. acetylcholinesterase inhibitors (Group
96 3); all other medicines with no known sedative properties (Group 4). Drugs included in groups 1,2
97 and 3-4 were assigned sedative ratings of 2, 1 (Table 2) and 0 respectively. Sedative load was
98 calculated as the sum of the sedative ratings at an individual level, for regularly used drugs.
99 Sedative Load (SL) scores of 0, 1-2 and 3 indicated no, low and high sedative load respectively.

100 The sedative load model was first published in 2003 and was updated in 2011.^{3,11} In our
101 study, this model was assessed and modified to include drugs taken by participants in this study
102 and to reflect the current knowledge about sedative effects of drugs. Two experienced clinical
103 pharmacists (IM,JP) independently consulted, reviewed and amended scores for the original updated
104 list of drugs¹¹ using standard and widely accepted reference sources e.g. product characteristics (SmPC)
105 information, and Maudsley Prescribing Guidelines²³. Relevant MEDLINE articles²⁴⁻²⁶ informed the
106 scoring of drugs not included on the list. Scores were reviewed by an experienced psychogeriatrician
107 and disagreements were resolved by consensus. Drugs included in our analysis with respective
108 scoring are listed in Table 2.

109

110 **Frailty Measures**

111 Phenotype frailty was operationalized using population-specific cut-points following the
112 methodology of Fried and colleagues¹³. This was done owing to differences in the assessments of

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

125 Additionally, a frailty deficit index (FI) was constructed using 40 self-reported health
126 deficits from the TILDA home interview followed previously published methodology (Appendix
127 1).^{16,29} The 40 deficits were associated with poor health, had a prevalence of 5-80%, were
128 distributed across several health domains and were associated with advancing age.¹⁶ Each deficit
129 was coded as present (1) or absent (0). The total was then summed and divided by 40. This
130 produced index scores between 0.0 and 1.0. List of 40 deficits included in FI is in Appendix.

131

132 **Demographic, Health and Lifestyle Measures**

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

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

148

149 **Statistical analyses**

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

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

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

162

163 **RESULTS**

164 **Characteristics of the study population and sedative load (SL)**

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

168 by 668 (19.4%) participants. Mean (SD) sedative load was 0.41 (± 1.00 ; range 0 to 9). Sedative load
169 was higher in women (0.50 [± 1.09], $p \leq 0.001$), than in men (0.32 [± 0.88]) and highest in the 75-84
170 years group (0.51 ± 1.11) compared to those aged 65-74 years (0.36 ± 0.93) or ≥ 85 years, (0.48
171 ± 0.97) respectively; $p \leq 0.001$. Detailed characteristics of this cohort by SL are provided in Table 1.

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

177

178 **Prevalence of frailty**

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

189

190 **The relationship between frailty and sedative load (SL)**

191 Mean SL was independently associated with frailty using both the frailty phenotype and FI
192 models as shown in (Figure 1. In unadjusted analyses, frail (OR 2.08, 95%CI 1.70-2.54) and prefrail
193 (OR 1.63, 95%CI 1.43-1.86) participants were significantly more likely to use medicines with
194 sedative properties than non-frail participants. After adjustment for all listed variables in Table 1,
195 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 ($\beta=0.30$; $p<0.001$. $B=2.54$; 95% CI 2.15-2.92). The adjusted model for all covariates listed in
200 Table 1, explained 10.4% of the variance ($R^2=0.104$, $F(10.72)=124.64$, $p\leq 0.001$) and the association
201 between SL and the FI score was significant at $p\leq 0.001$ ($B=1.77$; 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 comorbidities 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 study³ but
218 differs from the Australian study⁸, 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

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

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

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

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

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

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

275

276 **CONCLUSIONS**

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

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

283

284 **ACKNOWLEDGEMENTS**

285 Support for this study was provided by Irish Life (Grant No D02155), Atlantic Philanthropies
286 (D02175), and the Irish Government Department of Health and Children (G01529).

287 The authors would like to acknowledge the participants in the study, the members of the TILDA
288 research team, the study nurses, and administrators.

289 Authors would specially like to thank Professor Brian Lawlor, MD of Department of Psychiatry,
290 Trinity College Dublin, Ireland for his help in reviewing independently the sedative load categorisation.

291

292 **CONFLICT OF INTEREST**

293 The authors declared no conflict of interest.

294

295 **AUTHOR CONTRIBUTIONS**

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

301

302 **REFERENCES**

303

304 1 Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. *Lancet*.
305 2007 Jul 14;370(9582):185-91.

306

307 2 McLachlan AJ, Pont LG. Drug metabolism in older people – a key consideration in achieving optimal
308 outcomes with medicines. *J Gerontol A Biol Sci Med Sci*. 2012 February;67A(2): 175-180.

309

310 3 Taipale HT, Bell JS, Uusi-Kokko M et al. Sedative load among community-dwelling people aged 75 years and
311 older. *Drugs Aging* 2011;28(11):1-13.

312

313 4 Bourin M, Briley M. Sedation, an unpleasant, undesirable and potentially dangerous side-effect of many
314 psychotropic drugs. *Hum Psychopharmacol Clin Exp* 2004; 19: 135–139.

315

316 5 What's to blame for falls and fractures? Poor sleep or the sleeping medication?: Comment on

317 "Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents".
318 Widera E. JAMA Intern Med. 2013 May 13;173(9):761-2.
319
320 6 Hanlon JT, Horner RD, Schmader KE et al. Benzodiazepine use and cognitive function among community-
321 dwelling elderly. Clin Pharmacol Ther. 1998 Dec;64(6):684-92.
322
323 7 Gray SL, LaCroix AZ, Hanlon JT et al. Benzodiazepine use and physical disability in community-dwelling
324 older adults. J Am Geriatr Soc. 2006 Feb;54(2):224-30.
325
326 8 Gnjdic D, Le Counteur DG, Hilmer SN et al. Sedative load and functional outcomes in community-dwelling
327 older Australian men: the CHAMP study. Fundam Clin Pharmacol. 2014 Feb;28(1):10-9..
328
329 9 Hilmer SN, Gnjdic D. The effect of polypharmacy in older adults. Clin Pharmacol Ther. 2009 Jan;85(1):86-8.
330
331 10 Taipale HT, Hartikainen S, Bell JS. A comparison of four methods to quantify the cumulative effect of
332 taking multiple drugs with sedative properties. Am J Geriatr Pharmacother. 2010;8:460-471.
333
334 11 Linjakumpu T, Hartikainen S, Klaukka T et al. A model to classify the sedative load of drugs. Int J Geriatr
335 Psychiatry. 2003 Jun;18(6):542-4.
336
337 12 Clegg, A, Young J, Iliffe S et al. Frailty in elderly people. Lancet 2013; 381: 752-62.
338
339 13 Fried LP, Tangen CM, Walston J et al. Frailty in Older Adults: Evidence for a Phenotype. J Gerontol A Biol
340 Sci Med Sci. 2001 Mar;56(3):M146-56.
341
342 14 Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment—A review of the evidence and
343 causal mechanisms. Ageing Res Rev. 2013 Jul 4;12(4):840-851.
344
345 15 Avila-Funes JA, Amieva H, Barberger-Gateau P et al. Cognitive impairment improves the predictive
346 validity of the phenotype of frailty for adverse health outcomes: the three-city study. J Am Geriatr Soc. 2009
347 Mar;57(3):453-61.
348
349 16 Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci.
350 2007 Jul;62(7):722-7. Review.
351
352 17 Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. Eur J Clin
353 Pharmacol. 2013 Mar;69(3):319-26.
354
355 18 Gnjdic D, Hilmer SN, Blyth FM et al. High-risk prescribing and incidence of frailty among older
356 community-dwelling men. Clin Pharmacol Ther. 2012 Mar;91(3):521-8.
357
358 19 Taipale HT, Bell JS, Gnjdic D et al. Muscle strength and sedative load in community-dwelling people aged
359 75 years and older: a population-based study. J. Gerontol. A Biol. Sci. Med. Sci. (2011) 66 1384-92.
360
361 20 Taipale HT, Bell JS, Gnjdic D et al. Sedative load among community -dwelling people aged 75 years and
362 older: association with balance and mobility. J. Clin. Psychopharmacol. (2012) 32 218-224.
363
364 21 Kearney PM, Cronin H, O'Regan C et al. Cohort profile: the Irish Longitudinal Study on Ageing. Int J
365 Epidemiol. 2011;40:877-884.
366
367 22 WHO Collaborating Centre for Drug Statistics Methodology (www.whooc.no/atc) (accessed on 25/09/2013).
368
369 23 Taylor D (ed). The Maudsley Prescribing Guidelines in Psychiatry, 11th Ed. Wiley-Blackwell 2012.
370
371 24 Leucht S, Cipriani A, Spineli L et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in
372 schizophrenia: a multiple-treatments meta-analysis. Lancet 2013;382(9896):951-62
373
374 25 Gao K, Ganocy SJ, Gajwani P et al. J Clin Psychiatry. 2008 Feb;69(2):302-9. A review of sensitivity and
375 tolerability of antipsychotics in patients with bipolar disorder or schizophrenia: focus on somnolence.

373 26 Ananth J, Parameswaran S, Gunatilake S. Side effects of atypical antipsychotic drugs. *Curr Pharm Des.*
374 2004;10(18):2219-29,

375 27 O'Halloran AM, Finucane C, Savva GM et al. Sustained Attention and Frailty in the Older Adult Population.
376 *J Gerontol B Psychol Sci Soc Sci* 2013: doi:10.1093/geronb/gbt009.
377

378 28 Savva GM, Donoghue OA, Horgan F et al... Using timed up-and-go to identify frail members of the older
379 population. *J Gerontol A Biol Sci Med Sci.* 2013 Apr;68(4):441-6.
380

381 29 Searle S, Mitnitski A, Gahbauer E et al. A standard procedure for creating a frailty index. *BMC Geriatr* 2008,
382 8:24.
383

384 30 Katz S, Ford AB, Moskowitz RW et al. 24 Studies of Illness in the Aged. The Index of ADL: A Standardized
385 Measure of Biological and Psychosocial Function. *JAMA.* 1963;185(12):914-919.
386

387 31 Lawton, M.P., & Brody, E.M. (1969). Assessment of older people: Self-maintaining and instrumental
388 activities of daily living. *The Gerontologist*,9(3), 179-186.
389

390 32 Folstein MF, Folstein SE, McHugh PR; "Mini-mental state". A practical method for grading the cognitive
391 state of patients for the clinician. *J Psychiatr Res.* 1975 Nov;12(3):189-98.
392

393 33 Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies
394 Depression (CES-D) scale. *J Clin Psychol.* 1986 Jan;42(1):28-33.
395

396 34 Collard RM, Boter H, Schoevers RA et al. Prevalence of frailty in community-dwelling older persons: a
397 systematic review. *J Am Geriatr Soc* 2012; 60: 1487-92.
398

399 35 Wolfson L, Judge J, Whipple R et al. Strength is a major factor in balance, gait, and the occurrence of falls. *J*
400 *Gerontol A Biol Sci Med Sci.* 1995 Nov;50 Spec No:64-7.
401

402 36 Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (RAIL) predicts outcomes in middle
403 aged Aferican Americans. *J Nutr Health Aging.* 2012 Jul;16(7):601-8.
404

405 37 Woo J, Leung J, Morley JE.. Comparison of frailty indicators based on clinical phenotype and the multiple
406 deficit approach in predicting mortality and physical limitation. *J Am Geriatr Soc.* 2012 Aug;60(8):1478-86.
407

408 38 Hilmer SN, Mager DE, Simonsick EM et al. A drug burden index to define the functional burden of
409 medications in older people. *Arch Intern Med* 2007;167:781-7.
410

411 39 Qato DM, Schumm LP, Johnson M et al. Medication data collection and coding in a home-based survey of
412 older adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*
413 2009;64B(S1):i86—93.
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430

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

| | | Total Population (n=3,446) [n(%)] | Sedative Load [n(%)] | | | P-value |
|--|-------|---|----------------------|-------------------|---------------|---------|
| | | | (n=2,778) 0 | (n=495) 1 or 2 | (n=173) ≥3 | |
| Age (Yrs) | 65-74 | 2,137 (62.0) | 1,771 (82.9) | 279 (13.1) | 87 (4.1) | <0.001 |
| | 75-84 | 1,091 (31.7) | 843 (77.3) | 172 (15.8) | 76 (7.0) | |
| | ≥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 - Cardiovascular 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)

437

| 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)

438
439

440

441
442
443
444

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

447

448

| 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) ** |

449

450 I/ADL – Instrumental/Activities of Daily Living.

451 MMSE – Mini-Mental State Examination.

452 CES-D – Center for Epidemiological Studies –Depression scale.

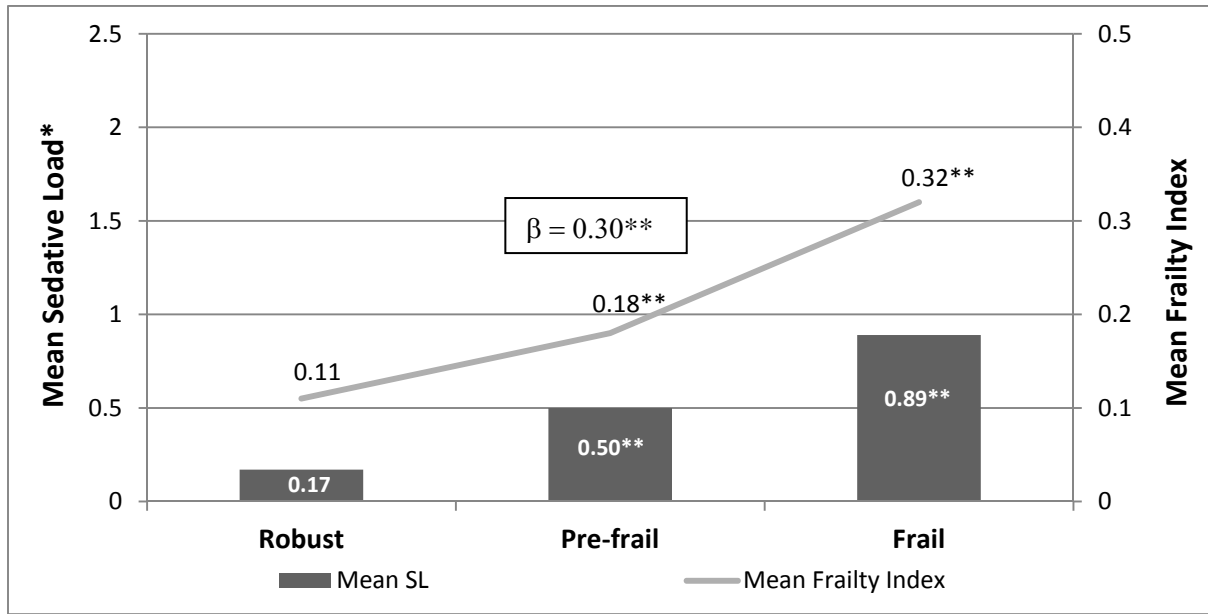
453 HADS-A – Hospital Anxiety and Depression Scale –Anxiety schedule.

454 *p<0.05, **p<0.001

455

456

457



458

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

461 **p<0.001

462

463

464

465

466

467

468

469

470

471

472

473

474

475

476

477

478

479

480

481

482

483

484

485

486

487

488

489

490

491

492

493

494

495

496 **Appendix I.** Adjusted model of association between the **modified** sedative load (SL) score
 497 and frailty phenotype status (n=1,718).
 498

| 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 |

499
 500
 501
 502
 503

504 **Appendix 2.** Adjusted model of association between the **original** sedative load (SL) score
 505 and frailty phenotype status (n=1,718).
 506

| 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 |

507