Elderly Benzodiazepine Users at Increased Risk of Activity Limitations: Influence of Chronicity, Indications, and Duration of Action-The Three-City Cohort.

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Word count: 3759

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Acknowledgment:

The 3C Study is conducted under a partnership agreement between the Institut National de la Santé et de la Recherche Médicale (Inserm), Victor-Segalen Bordeaux II University, and Sanofi- Aventis. The 3C-Study was also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, the Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of Aquitaine, Bourgogne and Languedoc-Roussillon, the Fondation de France, the Ministry of Research-Inserm Programme 'Cohorts and collection of biological material' and Novartis. The Lille Genopole was supported by an unconditional grant from Eisai.

This work was supported by the "ANR - Agence Nationale de la Recherche - The French National Research Agency" under the "Programme National de Recherche en Alimentation et nutrition humaine", project "COGINUT ANR-06-PNRA-005" and under the "Programme Longévité et vieillissement", project 07-LVIE-004" and 07-LVIE 003 01 and by the Institut de Recherche en Santé Publique (IReSP), Paris, France.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest:

Authors report no conflict of interest. No Disclosures to Report

Authors' contributions:

Study concept and design: IC, TM and MLA. Acquisition of data: KP, OR and CB. Analysis and interpretation of data: all authors. Statistical analysis: IC. Drafting of the manuscript: IC. Critical revision of the manuscript for important intellectual content: TM, KP, JN, IJ, AE, OR,

CB, KR and, MLA. Obtained funding: CB and KR. Study supervision: KR and MLA. All authors read and approved the final manuscript.

Keywords: Benzodiazepines, Activity of daily living, Aging, Longitudinal study, Random-effect model.

Abstract

Objective: To examine the cross-sectional and longitudinal associations between benzodiazepine use and daily activity limitations, according to drug indications and duration of action.

Design: Prospective cohort study.

Setting: Population-based 3-city study

Participants: 6 600 participants aged 65 years and over included between 1999 and 2001 and followed after 2, 4 and 7 years.

Measurements: Benzodiazepine users were separated into hypnotic, short-acting anxiolytic and long-acting anxiolytic users and compared with non users. Three outcomes were examined assessing restrictions in mobility, instrumental activities of daily living (IADL) and social participation.

Results: In multivariate simple or mixed logistic models adjusted for socio-demographic variables, impairments and comorbidity and for anxiety, insomnia and depression, hypnotic benzodiazepines were moderately associated with mobility limitation prevalence and IADL limitation incidence. Short-acting and long-acting anxiolytics were associated with IADL limitation prevalence and with mobility limitation prevalence and incidence and long-acting anxiolytics were also associated with IADL limitations incidence. Chronic benzodiazepines users were at a marked risk of developing restrictions for the three outcomes (odds ratio 1.71 (95% confidence interval (CI), 1.23-2.39) for mobility, 1.54 [95%CI, 1.14-2.10] for IADL and 1.74 [95%CI, 1.23-2.47] for participation limitations).

Conclusions: Benzodiazepine users are at increased risk of activity limitations regardless of the duration of action or indication. Chronic use of benzodiazepines should be avoided in order to extend disability-free survival.

Because of their extensive use and well-known side effects, the safety of benzodiazepines has received particular attention in older people. Benzodiazepines are usually prescribed for their sedative, anxiolytic, hypnotic, and muscle-relaxant effects. However they can produce excessive sedation, anterograde amnesia and motor coordination deficits and long-term usage induces problems of tolerance (decreasing pharmacological effect over time) and physical dependence (1). The likelihood of such adverse neurological reactions increases with age due to depletion of the neurotransmitter system, hormonal changes, decreased cerebral availability of glucose and oxygen, possibly greater penetration of drugs into the central nervous system (2) but also pharmacodynamic alterations with a decreased renal clearance and hepatic metabolism leading to increased elimination time. As a consequence the use of benzodiazepines is an established risk factor for falls (3-5) and hip fractures (6-9) in the elderly as well as for driving impairment and motor vehicle collisions (10). More controversially, new elderly users were recently found at increased risk of incident dementia (11) while the risk decreased after discontinuation in former users (12) and chronic users were found at risk of cognitive impairment but not cognitive decline (13).

Together these findings suggest a possible adverse effect on daily activities that require physical and cognitive capacities. However given that anxiety disorders (14) and poor sleep quality (15, 16) are also associated with incident activity limitations in the community-dwelling population, the global risk-benefit balance of treatment with benzodiazepines remains to be assessed. Increasing disability-free life expectancy and promoting good social functioning and participation for older people are foreground goals in aging populations; yet few studies have analyzed the effects of benzodiazepines on daily activity limitations (17-21).

Furthermore these studies have several methodological limits: i) not taking into account temporality between the exposure and the outcome and possible reverse causality ii) insufficient control of indication confounders (sleep and anxiety disorders) iii) not taking into

account pharmacological and pharmacokinetic properties of the drugs and the chronicity of their use and iv) not exploring the differential effects according to the degree of severity of the activity limitations.

The purpose of this study was to examine the cross-sectional and longitudinal associations between benzodiazepine use and activity limitations in a large elderly community-dwelling cohort, for which information on a large number of potential confounding factors including sleep and anxiety disorders was available. The analyses are based on three scales corresponding to different activity and participation restrictions and focus on the influence of benzodiazepine indications (hypnotic and anxiolytic) and duration of action (short- and long-acting).

Methods

Study sample

Subjects were recruited as part of a multi-site cohort study of community-dwelling persons aged 65 years and over from the electoral rolls of three French cities (Bordeaux, Dijon and Montpellier) between 1999 and 2001 (22). The study protocol was approved by the Ethical Committee of the University-Hospital of Bicêtre (France) and written informed consent was obtained from each participant. A standardized evaluation with a face to face interview and clinical examination was undertaken at baseline, 2, 4 and 7 years. Of the 9080 dementia-free participants included in the cohort, 6600 were included in the cross-sectional analysis and 5766, 3484 and 5651 in the longitudinal analyses of the incidence of participation restriction, mobility and instrumental activities of daily living (IADL) limitations, respectively (*flow-chart, figure 1*).

Compared with the analyzed sample, those not included in the cross-sectional analysis were more frequently benzodiazepine users, female, older, living alone, had a lower

education, lower income, cognitive impairment, cardiovascular and non cardiovascular chronic pathologies, depression, insomnia, anxiety, and hearing impairment ($p<0.0001$). They also had more visual impairment ($p=0.03$), baseline mobility, IADL and participation restriction ($p<0.0001$).

Outcomes

This study focuses on the two domains of activity limitations and participation restriction as defined by the International Classification of Functioning, Disability, and Health (23). Activity limitations were evaluated using two validated self-reported outcomes which correspond to different degrees of severity (24) and are sensitive to changes in this community-dwelling population. Mobility was assessed according to the Rosow and Breslau scale (25) which evaluates ability to do heavy housework, walk half a mile, and climb stairs. The Lawton-Brody IADL scale was used to assess individual ability to perform complex tasks: using the telephone, managing medication and money, using transport, shopping, and for women only, preparing meals and doing housework and laundry (26). For each outcome, participants indicating inability to perform one or more activities without help were considered as having mobility or IADL limitations. Participation restriction was assessed with a single question evaluating if participants were confined to bed, home or neighborhood.

Benzodiazepine exposure

At baseline and follow-up examinations, the general questionnaire included an inventory of all drugs used during the preceding month. To reduce underreporting, participants were asked to provide medical prescriptions, drug packages and any other relevant material. The names of the drugs were systematically coded using the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system. Hypnotic benzodiazepines being mainly short-acting drugs in our sample, benzodiazepines used at baseline were separated into hypnotics, short-acting anxiolytics (half-life time <20h) and long-acting anxiolytics (half-life

time ≥ 20h) (*Table 1*). Participants taking both anxiolytics and hypnotics at baseline were excluded (n=137) due to the small numbers of events for this group. To differentiate the effect of a chronic use from an occasional use, benzodiazepine intake was also considered at both inclusion and two-year examination separating participants who began the treatment at two years ("beginning group"), those reporting benzodiazepine use at baseline but not at two years ("discontinuing group"), and those reporting benzodiazepine use at both examinations ("continuing group"). They were compared with those reporting no intake of benzodiazepine neither at baseline nor at two years ("never users").

Baseline socio-demographic and clinical variables

The standardized interview included questions on socio-demographic characteristics, alcohol consumption, and visual and hearing impairments. The number of chronic diseases was calculated including: hypertension (>160/95 mm Hg or treated), diabetes (fasting glycemia> 7mmol/l or treated), respiratory diseases (asthma or chronic bronchitis), dyspnoea, thyroid disease, and cancer. Cardiovascular pathologies were considered separately and included stroke, angina pectoris, myocardial infarction, cardio-vascular surgery, arrhythmia, heart failure, and peripheral artery disease.

Cognitive impairment was defined as a Mini Mental State Examination (MMSE)(27) score <24. Participants with a current major depressive episode (diagnosed with the Mini International Neuropsychiatric Interview (28)) or a Center for Epidemiologic Studies–Depression scale (29) score ≥16 were classified as having depressive symptomatology. Current use of antidepressants was defined from reported drugs. Spielberger's State-Trait Anxiety Inventory was used to measure trait anxiety symptoms (30). In the absence of a validated cut-off score in the elderly population, the highest score tertile was compared to the lowest two. Insomnia was assessed by three specific questions: difficulties in initiating sleep, several awakenings during the night and early morning awakening without going back to

sleep. Participants declaring to have "frequently" or "often" at least two complaints were classified with insomnia complaints (31).

Statistical analyses

Comparison of baseline characteristics between treatment groups was performed using Chi-square tests. For each outcome (mobility, IADL and participation restriction), baseline cross-sectional associations with benzodiazepine treatment were tested separately using logistic regression models. To avoid reverse causality and clarify temporality, the longitudinal associations were established for subjects free of activity limitations at baseline. The exposure was defined firstly as the use of benzodiazepines at baseline (categorized according to indication and duration of action) and secondly as the patterns of the benzodiazepine use during the first two years of follow-up. Longitudinal analyses were performed using mixed logistic models (SAS procedure GLIMMIX with maximum likelihood estimation by adaptive Gaussian quadrature method) which take into account the within-subject response correlations (between repeated evaluations of activity limitations) (32) and possible reversion to normal functional state.

To control confounding effects, three nested models were performed for cross-sectional and longitudinal analyses. Model 0 was adjusted for gender, centre and age and included also for longitudinal analyses time from baseline and time*age interaction. Multivariate models included baseline covariates that were associated with the outcomes ($p<0.15$ in Model 0). Model 1 was further adjusted for socio-demographic variables, cognitive, hearing, and visual impairments and comorbidity and Model 2 for possible indication confounders e.g. insomnia, anxiety symptoms, depression and antidepressant use. Finally three group comparisons were performed using post-hoc contrasts with a Bonferroni adjustment for multiple comparisons: any benzodiazepines *vs.* none, hypnotic *vs.* any anxiolytic benzodiazepines and short-acting

vs. long-acting anxiolytic benzodiazepines. All analyses were conducted using the statistical software SAS version 9.3 for Windows.

Results

Cross-sectional analysis

Within this elderly community-dwelling population of 6600 participants 18.1% reported benzodiazepine use at inclusion: 5.2% hypnotic (0.6% long-acting hypnotic), 6.9% short-acting anxiolytic, and 6.0% long-acting anxiolytic. Table 2 provides baseline comparisons of treatment groups in terms of the potential confounders. Overall benzodiazepines were more frequently reported in women, participants aged 75 years and over, with low incomes, cardiovascular pathologies, two or more non cardiovascular diseases, and a visual impairment.

Table 3 shows the associations of benzodiazepines intake with current activity limitations. In Model 0 adjusted for center, age and gender, a significant association was found between anxiolytic use (irrespective of the half-life) and any activity limitations or participation restriction. The same association was observed for hypnotics, but this was only significant with mobility limitations. However the strength of the associations decreased when the models were further adjusted for socio-demographic variables, impairments and comorbidity (Model 1) and for possible indication confounders (Model 2). In this fully adjusted model, the three treatment groups remained significantly associated with odds of having mobility limitations (odds ratio (OR) between 1.31 and 1.57) while both long- and short-acting anxiolytics were associated with IADL limitations (OR of 1.43 and 1.62, respectively). No significant association was found for participation restriction.

In post-hoc analysis a significant difference was only found between benzodiazepine and non-benzodiazepine users for mobility (Wald $\chi^2[1]=19.4830$; p adjusted for multiplicity<0.0001) and IADL limitations (Wald $\chi^2[1]=6.6212$; p adjusted for multiplicity =0.03).

Longitudinal analysis

Of the 6063 subjects included in the longitudinal study, 4179 (68.9%) never took benzodiazepines (hypnotic or anxiolytic) throughout the 7-year follow-up. Of the 1067 participants taking benzodiazepines at baseline, 681 (63.8%) continued at each wave of the follow-up, 110 (10.3%) took benzodiazepines only once at baseline and the remaining 276 (25.9%) took intermittently benzodiazepines. The same rates were observed for those treated with hypnotics at baseline (n=305): 61.3% continued at each wave to take hypnotics whereas 10.2% stopped taking any benzodiazepine after baseline. Of the participants treated at baseline, only 117 (11.0%) changed benzodiazepine category during the follow-up.

As expected over the 3 follow-up waves, the prevalence of activity limitations increased with the cohort aging, ranging from 4.1% to 12.7% for participation restriction, from 34.2% to 50.2% for mobility limitations, and from 5.4% to 19.7% for IADL limitations.

Over the 7-year follow-up the number of incident cases was 820 (14.2%) for participation restriction, 2199 (63.1%) for mobility limitations, and 1179 (20.9 %) for IADL limitations with a reversibility rate of 16.2%, 30.2% and 15.4%, respectively.

In the fully adjusted model assessing the effects of baseline benzodiazepine intake on incident activity limitations (*Table 4*), hypnotic use was specifically associated with IADL limitations (55% odds increase), short-acting anxiolytic use with mobility limitations (60% odds increase), and long-acting anxiolytic group with both mobility and IADL limitations (58% and 70% odds increase, respectively). In post-hoc analysis a significant difference was found

between any benzodiazepine and no benzodiazepine groups for the three outcomes (t=-2.37, df=9034, p-value adjusted for multiplicity = 0.0538; t=-3.21, df=5544, p-value adjusted for multiplicity =0.004 and t=-2.42, df=8824, p-value adjusted for multiplicity=0.046 for participation, mobility and IADL restriction, respectively) and a non-significant difference between short-acting and long-acting anxiolytics for IADL limitations (t=-2.17, df=8824, p-value adjusted for multiplicity=0.09).

We then examined activity limitations according to the pattern of the benzodiazepine use during the first two years. Due to lower numbers overall benzodiazepine treatment was only considered. Of the 5890 participants with both baseline and two-year examinations, 540 (8.9%) were in the "beginning group", 169 (2.8%) in the "discontinuing group" and 868 (14.3%) in the "continuing group". In this last group, 25.0% took hypnotics, 36.2% short-acting anxiolytics and 26.7% long-acting anxiolytics at both waves.

In the multi-adjusted models irrespective of the three outcomes, there was a clear increased odds (between 49% and 78%) of developing restriction for the three outcomes in the "continuing group" compared with the "never users" whereas no significant increased risk was found for the "discontinuing group" (*table 5, Model 2A*). In the beginners, the odds was significantly increased for participation restriction as well as more slightly for mobility limitations (by 110% and 33% respectively). To avoid possible inverse causality during the first two years we performed an additional analysis restricted to participants free of activity limitations at both baseline and two-year visit (*Table 5, Model 2B*) and we confirmed the high significant increase in activity limitations for the "continuing group" irrespective of the outcome. To illustrate this result an individual curve of predicted probabilities of having activity limitations over time is given in *Figure 2* for the three outcomes.

No interaction was found in the cross-sectional and the longitudinal multivariate analysis (Model 2) between benzodiazepine use and depressive, anxiety symptoms or insomnia

complaints irrespective of the activity limitation outcome. The associations did not change when anxiety symptoms and insomnia were taken as continuous scores instead of binary criteria to control for possible residual confounding of severity level (data not shown).

Discussion

In this large prospective study, 18% of these community-dwelling older adults reported taking benzodiazepines, which were predominantly anxiolytics (71%). Overall, our results provide further evidence for a 50 to 80% increased odds of developing activity limitations with a chronic use of benzodiazepines, which remained significant after adjustment for a large range of other possible codeterminants. This suggests that benzodiazepines themselves rather than the underlying burden of illness are a possible source of these activity limitations. Several arguments are consistent with a possible causative effect of benzodiazepines on activity limitations; i) we showed that activity limitations may be reversible after benzodiazepine treatment was discontinued; ii) a possible cumulative effect over the follow-up period is also suggested by the higher significant associations observed with chronic use; iii) a plausible causal pathways exists involving intermediate factors such as falls (3-5), hip fractures (6-9), driving impairment (10) and cognitive impairment (11-13); iv) the temporality of the associations has been addressed in our longitudinal analyses.

To our knowledge, our study is the first to consider both the main pharmacological effect of the medication (hypnotic or anxiolytic) and their half-life (short- versus long-acting). Our data show that i) hypnotic benzodiazepines (predominantly short-acting) were moderately associated with mobility limitation prevalence and IADL incidence; ii) long-acting anxiolytic benzodiazepines were strongly associated with both mobility and IADL limitation prevalence and incidence; iii) short-acting anxiolytic benzodiazepines were strongly associated with IADL limitation prevalence and mobility limitation prevalence and incidence.

Duration of action and indication

Only few studies have analyzed the effects of benzodiazepines on activity limitations taking into account duration of action. In a cross-sectional analysis, Ried et al found that benzodiazepines dispensed during the last year were positively associated with a total score including both IADL and ADL limitations (20), however they did not distinguish between short- and long-acting drugs. Gray et al found a significant multiple adjusted association of benzodiazepine use with physical functioning but not with ADL (18); however in a second larger study they found a significant association with mobility and ADL (19), the risk for ADL limitations being greater for short-acting agents. In another longitudinal cohort, Boudreau et al did not find an association with mobility (17). These last three longitudinal studies used a similar methodology with time-varying exposure which analyzes the immediate or short-term effect. In a prognostic score of 4-year risk of physical activity and basic activity limitations, Sarkisian et al found a significant effect of benzodiazepines for both outcomes with a greater effect of short-acting drugs for physical activities (21). In our study, we did not find a difference between short- and long-acting anxiolytics for mobility limitations which thus indicates that not only users of long-acting but also short-acting anxiolytic benzodiazepines may be also at risk of moderate limitations. For IADL limitations the same effect was observed for prevalence although more significant for short-acting anxiolytics. However due to the cross-sectional associations we cannot exclude reverse causality and that IADL limitations could induce anxiolytic intake. Interestingly a very significant increase of 70% in incidence odds was found for long-acting anxiolytics, the post-hoc comparison with short-acting anxiolytics being nearly significant. This suggests that long-acting anxiolytics could be specifically linked with the onset of more severe limitations (21).

For hypnotics, the low number of cases taking long-acting hypnotics did not allow us to address this question. Differential effects were observed between cross-sectional and

longitudinal analyses for mobility (only significant in cross-sectional analysis) and IADL (only significant in longitudinal analyses) limitations. However, the moderate association with incidence of IADL but not mobility does not allow us to draw any definite conclusion about hypnotic drugs and further studies are still needed to evaluate their effects.

Different outcomes

Limitations in activities are typically assessed using mobility as well as both instrumental and basic ADLs which correspond to an increased gradient of severity (24). The analyses concerning basic ADL could not be performed in our sample due to the small numbers of subjects using benzodiazepines and presenting basic ADL (33). Overall we found a significant short-term (cross-sectional) and long-term (longitudinal) alteration of both mobility and IADL. We also observed a negative effect on the other domain of social participation (problems an individual may experience in involvement in life situations (23)) which was partly related to residual symptoms rather than to a treatment effect *per se*, the short term (*Table 3*) and long term (*Table 4*) effects becoming non-significant after adjusting for the psychiatric symptoms. This is in agreement with our previous observation that subjects with anxiety or depressive symptomatology were more likely to become socially restricted (14, 33). However, chronic use of benzodiazepines over two years was found to increase the odds of developing participation restrictions by more than 70% even after controlling for indication bias.

Irrespective of the outcome and as previously already observed in other longitudinal studies (34-36) the level of recovery from disability was relatively high in our cohort. To exclude reverse causality we selected people free of activity limitations at baseline; incident cases are thus newly disabled persons and potentially more reversible. However and in contrast with previous studies, we took into account this unstable disability using logistic mixed models.

Chronic use of benzodiazepines

Clinical guidelines generally recommend prescribing benzodiazepines to treat anxiety or insomnia that is severe, disabling and causing extreme distress. In our cohort and in spite of repeated recommendations aimed at limiting the maximum duration of prescription (37) more than 10% of the participants free of activity limitations at inclusion were still treated after two-year follow-up and this resulted in a marked increased odds of developing mobility and IADL limitations as well as participation restriction. This relationship was particularly robust when we restricted our analyses to participants free of activity limitations at both the inclusion and the two-year visits (*Figure 2*). This is in keeping with recommendations for limiting benzodiazepine use at the lowest effective dose for the shortest period of time (maximum 4 weeks) and of early intervention strategies to avoid chronic use. More efforts are required for training physicians in the skills of reduction and discontinuation of benzodiazepines (38, 39).

Limitations

The main concern with observational studies is indication bias which occurs when persons are prescribed drugs for a condition that is itself associated with the outcome of interest. The apparent associations with the drug may then be due to the medical condition for which it was prescribed rather than to the medication itself. Channeling bias may also occurred when comparing short- and long-acting benzodiazepines; short-acting drugs being generally considered as safer may be prescribed preferentially to frail patients. To reduce these biases we first adjusted the models for potential confounders including socio-demographic and behavioral characteristics, sensorial deficiencies, cognitive impairment and physical diseases (Model 1) and then for possible remaining symptoms of insomnia, anxiety and depression as well as antidepressant use (Model 2). However, we did not consider certain specific insomnia criteria including effects of diurnal sleepiness (fatigue or low energy, difficulties of attention, concentration) (40), although we were able to adjust for others (memory and mood disturbances). Spielberger's trait score was also shown to be correlated with depression (41)

and may not cover all anxiety types. When we studied the pattern of use during the first two years new anxiety cases or insomnia symptoms were not available during this period; therefore we were not able to adjust for these possible confounders which may affect the results concerning the "beginning group". Although such a large range of confounding factors has not been taken into account in previous studies, we cannot however, exclude possible residual confounding in our results notably due to chronic or acute pain. On the contrary, over-adjustments may also have occurred when cognitive impairment and psychiatric symptoms were added to the models. Because we did not have detailed information on prescribed dose, duration, and compliance we could not address the question of dose-effect relationship. Finally we excluded demented persons at inclusion to avoid unreliable responses to self-questionnaires which may have lead to an underestimation of the associations.

Strength

Our prospective study based on a large multicentric community sample permitted a dynamic evaluation of activity limitations using three scales with an increased gradient of severity and repeated examinations over 7 years. Our findings are thus more generalisable to the elderly population than those from clinical trials which generally select “healthy” samples without polymedicated older people. Benzodiazepine use was carefully assessed with presentation of medical prescriptions and drug packages and we took into account pharmacological properties and half-life. We studied both cross-sectional and longitudinal associations to distinguish short-term and prolonged effects, we adjusted for a large number of potentially confounders and we controlled for theoretical indication bias. In longitudinal analysis we could rule out the reverse causality by restricting the sample to people free of activity limitations at the time of benzodiazepine intake assessment.

Conclusions

Findings from this study suggest that the risks and benefits of using benzodiazepines (regardless of the duration of action) should be carefully considered in elderly patients avoiding chronic use. Benzodiazepines have rapid onset, relatively low toxicity, and anxiolytic potency but these benefits should be weighed against potential risk of motor impairment, dependence, and withdrawal symptoms. A more sensible prescription of benzodiazepines in community-dwelling elderly people could extend disability-free survival which is a most relevant outcome for elderly people.

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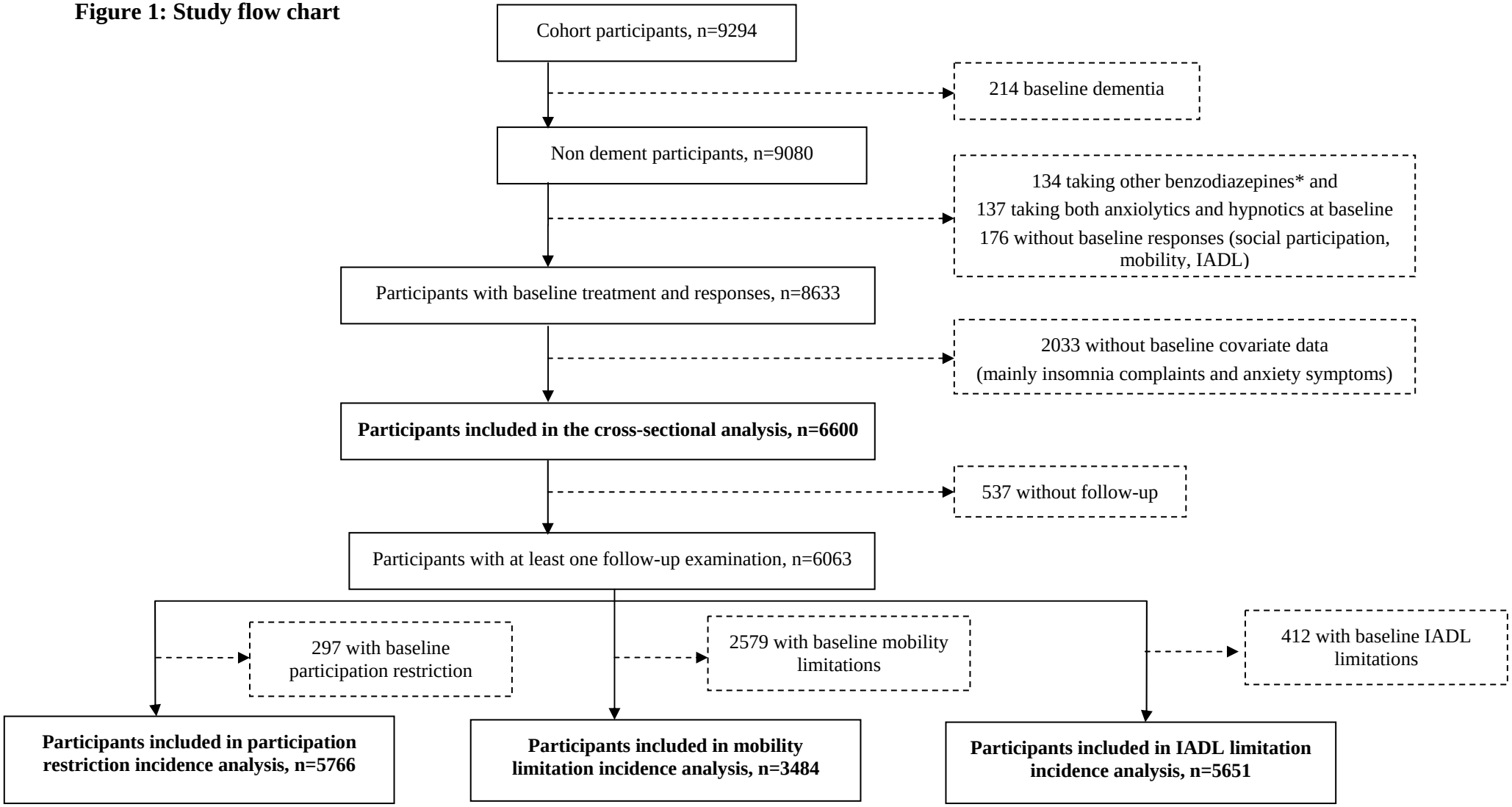
Figures

Tables

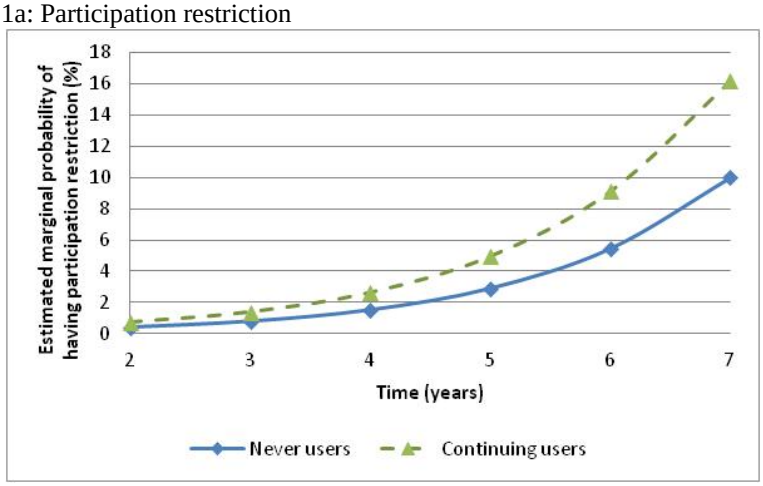
Figure 1: Study flow chart



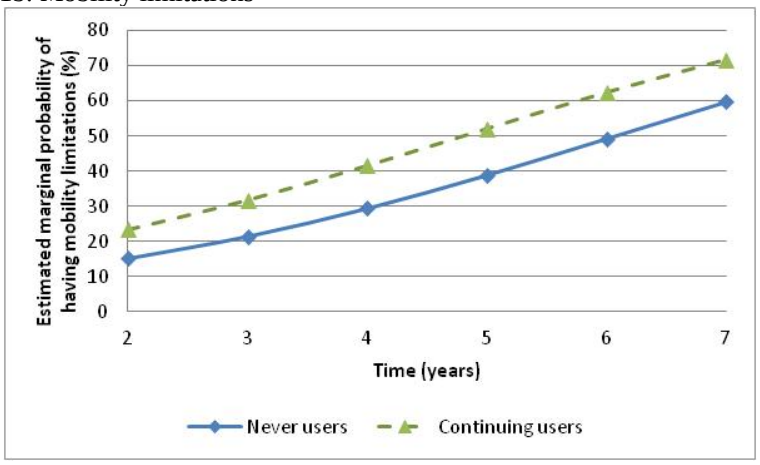
*exclusion of 134 participants using either clonazepam (anticonvulsant agent) or tetrazepam (muscle relaxant with a marketing authorization suspended in Europe in 2013)

Figure 2: Changes over time in the probabilities* of having activity limitations

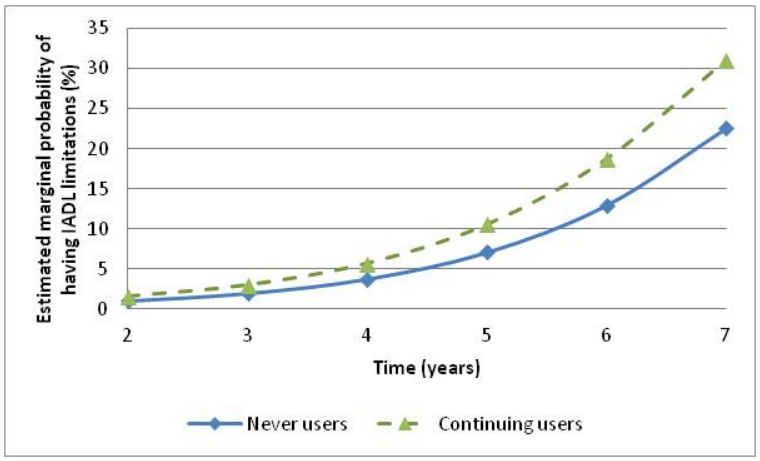
1a: Participation restriction



1b: Mobility limitations



1c: IADL limitations



* Marginal probabilities for a woman free of activity limitations at baseline and 2 years, aged of 80 years at inclusion and without any other risk factors (based on the estimated fixed parameters of the mixed logistic regression, Model 2B, Table 5)

Table 1: List of drugs used in the study*

Classes	Drug Names	Prevalence at baseline (%)† n=1192
Hypnotics	estazolam	0.34
	flunitrazepam	2.85
	loprazolam	0.84
	lormetazepam	1.51
	midazolam	0.00
	nitrazepam	0.76
	temazepam	0.42
	triazolam	0.25
	zolpidem	12.92
	zopiclone	9.23
Short-acting anxiolytics	alprazolam	6.12
	clotiazepam	0.17
	lorazepam	29.36
	oxazepam	4.87
Long-acting anxiolytics	bromazepam	21.22
	clobazam	1.34
	clorazepate	2.43
	chlordiazepoxyde	0.00
	diazepam	1.09
	ethyl loflazepate	0.50
	nordazepam	0.76
	prazepam	5.96

*exclusion of 134 participants using either clonazepam (anticonvulsant agent) or tetrazepam (muscle relaxant with a marketing authorization suspended in Europe in 2013)
† the sum of percents exceeds 100% as several participants used two drugs of the same class.

Table 2: Sample description at baseline

	Total (N=6600) %	No benzodiazepine (N=5408) %	Hypnotic* (N=343) %	Short-acting anxiolytic (N=456) %	Long-acting anxiolytic (N=393) %	Chi^2	df	P value
Sex (male)	41.3	44.6	29.7	23.3	27.0	137.03	3	<0.0001
Age								
65-69	25.5	26.8	19.2	16.4	24.2	81.58	9	<0.0001
70-74	34.2	34.9	26.5	30.5	34.1			
75-80	26.3	25.4	33.0	31.4	27.2			
80+	14.0	12.9	21.3	21.7	14.5			
Education (≤ 5 years)	22.8	22.2	22.7	24.3	29.0	10.44	3	0.015
Living alone	33.2	31.1	45.5	43.0	40.0	61.40	3	<0.0001
Income (> 1500 €/month)	68.3	70.0	60.4	59.9	60.6	43.44	3	<0.0001
Alcohol consumption								
0	19.2	18.3	18.4	26.3	24.9	35.98	6	<0.0001
1-36 g/day	72.1	72.5	74.0	67.3	70.5			
> 36g/day	8.7	9.2	7.6	6.4	4.6			
BMI								
Normal (<25)	47.6	46.9	45.5	54.0	50.9	13.77	6	0.03
Overweight (25-29)	39.7	40.4	41.4	34.6	34.6			
Obese (≥30)	12.7	12.7	13.13	11.4	14.5			
Number of non cardiovascular pathologies	34.9	35.8	27.7	32.0	30.8	22.59	6	0.0009
None	49.5	49.2	50.1	50.7	52.2			
1	15.6	15.0	22.2	17.3	17.0			
2+								

Cardiovascular pathology	27.9	26.3	34.7	37.3	33.6	41.40	3	<0.0001
Cognitive impairment (MMSE score <24)	4.2	4.0	5.8	5.5	5.1	5.50	3	0.14
Visual impairment†	14.8	13.5	19.5	21.9	19.6	38.52	3	<0.0001
Hearing impairment‡	7.4	7.1	6.7	10.1	9.2	7.73	3	0.05
Trait Anxiety (upper tertile)	33.9	30.0	44.3	54.8	51.9	199.02	3	<0.0001
Insomnia complaints	42.4	38.2	70.3	59.2	56.5	233.47	3	<0.0001
Depressive symptomatology	22.3	18.7	31.2	41.5	41.7	238.97	3	<0.0001
Antidepressant use	5.7	3.3	12.8	14.3	21.4	333.35	3	<0.0001
Participation restriction: home or neighborhood confined	5.6	4.6	9.0	9.9	10.2	48.67	3	<0.0001
Activity limitations: Mobility	43.4	39.7	58.3	64.9	56.2	172.81	3	<0.0001
Activity limitations: IADL	7.5	6.0	10.5	17.1	13.7	104.22	3	<0.0001

*Of the 343 participants taking hypnotic at baseline only 42 (12.2%) took long acting hypnotic.

†Visual impairment defined as having a corrected near visual acuity (Parinaud scale) of less than 2 or difficulties recognizing a familiar face at 4 meters.

‡ Hearing impairment defined as deafness or only able to hear a conversation when a single person speaks loudly.

Table 3: Cross-sectional association of benzodiazepine use and activity limitations, N=6600

	Model 0*			Model 1†			Model 2‡		
	OR (95%CI)	Wald Chi-Square	P value§	OR (95%CI)	Wald Chi-Square	P value§	OR (95%CI)	Wald Chi-Square	P value§
Participation restriction									
Hypnotic	1.44 [0.96;2.18]	3.05	0.08	1.34 [0.87;2.05]	1.76	0.18	1.14 [0.74;1.76]	0.34	0.56
Short-acting anxiolytic	1.51 [1.06;2.16]	5.21	0.02	1.31 [0.90;1.91]	2.01	0.16	1.01 [0.69;1.49]	0.003	0.96
Long-acting anxiolytic	1.96 [1.35;2.85]	12.50	0.0004	1.63 [1.09;2.44]	5.77	0.02	1.26 [0.84;1.89]	1.20	0.27
Mobility limitations									
Hypnotic	1.68 [1.32;2.13]	17.63	<.0001	1.57 [1.23;2.01]	12.98	0.0003	1.35 [1.05;1.74]	5.61	0.02
Short-acting anxiolytic	2.00 [1.61;2.49]	38.99	<.0001	1.89 [1.51;2.36]	31.27	<0.0001	1.57 [1.25;1.97]	14.8938	0.0001
Long-acting anxiolytic	1.75 [1.40;2.19]	23.70	<.0001	1.63 [1.29;2.05]	17.11	<0.0001	1.31 [1.03;1.66]	4.8824	0.03
IADL limitations									

Hypnotic	1.36 [0.93;1.99]	2.46	0.12	1.28 [0.87;1.90]	1.56	0.21	1.08 [0.73;1.61]	0.16	0.69
Short-acting anxiolytic	2.22 [1.66;2.96]	29.25	<.0001	2.00 [1.48;2.71]	20.55	<0.0001	1.62 [1.19;2.20]	9.31	0.002
Long-acting anxiolytic	2.16 [1.56;3.00]	21.16	<.0001	1.87 [1.32;2.63]	12.49	0.0004	1.43 [1.01;2.04]	3.96	0.05

*Model 0: adjusted for center, age and gender

†Model 1: adjusted for center, age, gender, living alone, educational level, income, BMI, visual impairment, hearing impairment, cognitive impairment, number of chronic non cardiovascular pathologies, cardiovascular pathology and alcohol consumption

‡Model 2: Model 1+ insomnia complaints, anxiety symptoms, depressive symptomatology and antidepressant use

§ df=1

IADL, instrumental activities of daily living; OR, odds ratio from logistic regression

Table 4: Longitudinal association of baseline benzodiazepine use and incident activity limitations (mixed logistic regression)

		Model 0*			Model 1†			Model 2‡		
	n	OR (95%CI)	t	P value§	OR (95%CI)	t	P value§	OR (95%CI)	t	P value§
Participation restriction, n=5766										
Hypnotic	281	2.17 [1.34;3.53]	3.13	0.002	1.84 [1.14;2.95]	2.52	0.01	1.52 [0.94;2.43]	1.72	0.08
Short-acting anxiolytic	369	2.06 [1.32;3.21]	3.19	0.001	1.69 [1.10;2.60]	2.37	0.02	1.28 [0.83;1.98]	1.12	0.26
Long-acting anxiolytic	326	2.63 [1.62;4.26]	3.92	<0.0001	2.14[1.34;3.42]	3.16	0.002	1.52 [0.94;2.44]	1.71	0.09
Mobility limitations, n=3484										
Hypnotic	128	1.34 [0.92;1.96]	1.51	0.13	1.28 [0.88;1.87]	1.30	0.19	1.19 [0.81;1.74]	0.87	0.38
Short-acting anxiolytic	150	1.81 [1.28;2.56]	3.35	0.0008	1.78 [1.26;2.51]	3.28	0.001	1.60 [1.13;2.26]	2.66	0.008

Long-acting anxiolytic	162	1.86 [1.32;2.61]	3.58	0.0003	1.82 [1.30;2.56]	3.47	0.0005	1.58 [1.12;2.24]	2.58	0.01
IADL limitations, n=5651										
Hypnotic	275	1.82 [1.21;2.73]	2.86	0.004	1.70 [1.14;2.54]	2.58	0.01	1.55 [1.03;2.32]	2.12	0.03
Short-acting anxiolytic	344	1.30 [0.88;1.90]	1.33	0.18	1.16 [0.79;1.69]	0.75	0.46	0.96 [0.65;1.41]	-0.20	0.84
Long-acting anxiolytic	315	2.56 [1.73;3.79]	4.69	<0.0001	2.21 [1.50;3.25]	4.00	<0.0001	1.70 [1.15;2.52]	2.65	0.008

* Model 0: adjusted for center, age, time, time*age and gender

†Model 1: adjusted for center, age, time, time*age, gender, living alone, educational level, income, BMI, visual impairment, hearing impairment, cognitive impairment, number of chronic non cardiovascular pathologies, cardiovascular pathology and alcohol consumption

‡Model 2: Model 1+ insomnia complaints, anxiety symptoms, depressive symptomatology and antidepressant use

§ p-value based on t-test with df=9034, 5544 and 8824 for participation restriction, mobility limitation and IADL limitation, respectively

IADL, instrumental activities of daily living; OR, odds ratio from mixed logistic model

Table 5: Patterns of benzodiazepine use during the first two years of follow-up and incident activity limitations (mixed logistic regression)

		Model 2A* Participants free of activity limitations at baseline (7 years of follow-up)				Model 2B* Participants free of activity limitations at baseline and 2 years (5 years of follow-up)		
	n	OR (95%CI)	t	P value‖	n	OR (95%CI)	t	P value¶
Participation restriction		n=5610				N=4917		
Beginning†	508	2.10 [1.44;3.07]	3.83	0.0001	422	1.57 [1.03;2.37]	2.11	0.04
Discontinuing‡	155	0.99 [0.48;2.05]	-0.03	0.97	131	1.05 [0.49;2.23]	0.12	0.90
Continuing§	796	1.78[1.28;2.46]	3.45	0.0006	664	1.74 [1.23;2.47]	3.11	0.002
Mobility limitations		n=3384				N=2040		
Beginning†	261	1.33 [1.01;1.74]	2.06	0.04	137	1.11 [0.77;1.62]	0.57	0.57
Discontinuing‡	87	1.29 [0.81;2.04]	1.07	0.29	44	0.80 [0.42;1.53]	-0.68	0.49

Continuing§	344	1.56 [1.21;1.99]	3.50	0.0005	178	1.71 [1.23;2.39]	3.15	0.002
IADL limitations		n=5494				N=4752		
Beginning†	491	1.18[0.84;1.65]	0.96	0.34	421	1.31 [0.92;1.88]	1.48	0.14
Discontinuing‡	149	1.14 [0.63;2.05]	0.44	0.66	119	0.76 [0.38;1.52]	-0.78	0.44
Continuing§	762	1.49 [1.13;1.96]	2.82	0.005	631	1.54 [1.14;2.10]	2.79	0.005

*Model 2A and 2B: adjusted for center, age, time, time*age, gender, living alone, educational level, income, BMI, visual impairment, hearing impairment, cognitive impairment, number of chronic non cardiovascular pathologies, cardiovascular pathology, alcohol consumption, insomnia complaints, anxiety symptoms, depressive symptomatology and antidepressant use. The reference group corresponded to the participants reporting no intake of benzodiazepine neither at baseline nor at 2 years.

†Beginning: treated with benzodiazepines at 2 years and not at inclusion

‡Discontinuing: treated with benzodiazepines at inclusion and not at 2 years

§Continuing: treated with benzodiazepines both at inclusion and 2 years

‖ p-value based on t-test with df=8980, 5511, 8772 for participation restriction, mobility limitation and IADL limitation, respectively

¶ p-value based on t-test with df=3796, 1630, 3656 for participation restriction, mobility limitation and IADL limitation, respectively

IADL, instrumental activities of daily living; OR, odds ratio from mixed logistic model