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Use of non-benzodiazepine hypnotics is associated with falls in nursing home residents: a longitudinal cohort study

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Abstract

Background

Falls and related injuries are common among older people, and several drug classes are considered to increase fall risk.

Aims

This study aimed to investigate associations between the use of certain drug classes and falls in older nursing home residents in Sweden, and relate these to different age groups.

Methods

Information on falls the previous year and regular use of possible fall risk drugs including non-benzodiazepine hypnotics (zopiclone and zolpidem) was collected from 331 nursing home residents during 2008-2011. Over the following six months the occurrence of serious falls, requiring a physician visit or hospital care, was registered. Associations between serious falls and drug use were compared between an older (≥ 85 years) and a younger group.

Results

An increased fall risk (Downton Fall Risk Index ≥ 3) was found in 93% of the study subjects (aged 65-101 years). Baseline data indicated an association between falls the previous year and regular use of non-benzodiazepine hypnotics ($p = 0.005$), but not with the other studied drug classes. During the following six months, an association between use of non-benzodiazepine hypnotics and serious falls in the older group ($p = 0.017$, Odds Ratio = 4.311) was found. No associations were found between the other studied drug classes and serious falls.

Discussion

These results indicate an association between falls and the use of non-benzodiazepine hypnotics, compounds that previously have been considered generally well tolerated in older people.

Conclusions

Caution is advocated when using non-benzodiazepine hypnotics regularly in older people living in nursing homes.

Keywords

Accidental falls – Frail elderly – Nursing homes – Hypnotics and Sedatives – Adverse effects – Longitudinal study

Introduction

Falls and fall-related injuries are common and well documented among older people, and a major cause of pain, disability, loss of independence and premature death [1]. Risk factors for falls in older people include increasing age, reduced mobility, previous falls, cognitive impairment and medication use [1,2]. For older people, the number of medications is associated with increased fall risk [3]. Minimisation of drug use and especially reduction of psychotropic medication is therefore included in fall prevention recommendations [2].

Moreover, instruments such as Beers Criteria [4-8] and STOPP (Screening Tool of Older Person's Prescriptions) Criteria [9,10] have been developed, where potentially inappropriate drugs for older people are listed. Beers Criteria list drugs and drug classes that are potentially inappropriate for older people with a history of falls or fractures, and STOPP Criteria list drugs that increase the risk of falls in older people. In these lists, several psychotropic drug classes are included, such as benzodiazepines [5-11], tricyclic antidepressants [6-8], selective serotonin re-uptake inhibitors (SSRI) [7,8], antipsychotics and anticonvulsants [7,8]. The recent versions of these instruments also include non-benzodiazepine hypnotics [7,8,10]. Among cardiovascular drugs, STOPP Criteria include vasodilators [9,10] and an earlier version of Beers Criteria included beta-blockers [5]. In Sweden, the National Board of Health and Welfare has produced a list of fall-risk-increasing drugs for patients aged 75 and older, which includes psychotropic or cardiovascular drugs [12].

Furthermore, some reviews and meta-analyses on medications associated with falls in older people highlight different psychotropic drug classes as fall risk drugs, mainly benzodiazepines [11,13], antidepressants [11,13,14], and sedatives/hypnotics [13,14]. One review also found an elevated fall risk related to use of antipsychotics [11], but in later

reviews this is questioned [13,14]. The fall risk associated with cardiovascular or antihypertensive drugs has been reported as uncertain [11,13,14].

Few recent studies have been published on associations between drug use and fall risk in older people living in nursing homes. Even in these studies, use of different psychotropic drugs such as antipsychotics [15-17], antidepressants [15], benzodiazepines [16,17] and non-benzodiazepine hypnotics [18] has been reported to be associated with an increased fall risk. However, none of these studies compared risks in different age groups, and the only study investigating non-benzodiazepine hypnotics [18] was performed in the US where zopiclone, the most commonly used non-benzodiazepine hypnotic in Europe, was not available. In addition, the latter study population was relatively young (age ≥ 50 years, mean age 81) compared to many populations of older people living in nursing homes. The aim of this study was therefore to investigate associations between falls and use of possible fall risk drug classes including non-benzodiazepine hypnotics (zopiclone and zolpidem) in older people living in nursing homes in Sweden in relation to age groups.

Methods

Study population

The Study of Health and Drugs in the Elderly (SHADES) was a longitudinal cohort study that included older people living in 12 different nursing homes in three areas in the south of Sweden (Jönköping, Linköping, and Eslöv). The overall aim of SHADES was to describe and analyse the morbidity, mortality, laboratory findings and pharmaceutical treatment of older people living in nursing homes to improve health care for this fragile patient group [19].

All residents living in the selected nursing homes were invited to participate in the study. When a resident in one of the nursing homes moved or died, the next person who moved in was invited to participate when the study nurse returned for the next follow-up visit. Between

2008 and 2011, in total 428 study subjects were included in SHADES. Individuals living in a nursing home only temporarily for palliative care or short-term rehabilitation were excluded, as well as persons with language difficulties or under the age of 65 years. Included study subjects were investigated every six months (±1 month) during the study period.

As study subjects were included during the whole study period, they had varying numbers of follow-up assessments. The study subjects available for six months follow-up (n=331) were included in this study. The numbers of study subjects included, excluded, or missing in the different parts of the study are illustrated in Figure 1.

Fig. 1 Flow chart of study subjects in the SHADES study

Methods of investigation

Study subjects were examined at baseline by specially trained study nurses who also collected data from patient records on current regular drug use, diagnoses and health care utilisation. Regular drugs were considered to be the drugs the patient was prescribed for continuous use on the day of data collection, whereas drugs taken as needed were not registered. Regular drugs were registered with codes according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system [20] and classified in possible fall-risk-increasing drug classes (antipsychotics, benzodiazepines, non-benzodiazepine hypnotics, antidepressants, antihypertensives, and vasodilators). The number of regularly used drugs, and the number of psychotropic drugs, defined as antipsychotics (ATC code N05A), anxiolytics (N05B), sedatives (N05C) and antidepressants (N06A) was calculated for each subject.

Diagnoses were collected with diagnosis codes according to the Swedish version of the International Classification of Diseases (ICD) – 10th version [21]. We defined dementia as any of the following ICD codes: F00 dementia in Alzheimer´s disease, F01 vascular

dementia, F02 dementia in other diseases classified elsewhere, F03 unspecified dementia, or G30 Alzheimer´s disease.

The in-person testing of study subjects was performed by the study nurses with assistance from the staff at the nursing home, and included measurement of weight, height and blood pressure. Blood pressure was measured three times at one-minute intervals in the right arm, while in a sitting position, and the mean value of the three measurements was used.

The Downton Fall Risk Index (DFRI) [22] was used to assess fall risk. DFRI is a composite risk index that takes into account several factors known to increase fall risk through assessment of 11 items giving a score between 0 and 11, where 3 or more is considered to indicate a higher fall risk. The first item in the DFRI is a question to the nursing home staff on whether the person has fallen during the last 12 months. The result from this question was used in the baseline analysis. Assessment with DFRI does not require cooperation from the study subject, but does need information from the staff.

The Mini Mental State Examination (MMSE) [23] was used to measure cognitive function. MMSE assesses cognitive function through a number of questions directed to the study subject, regardless of cognitive function. Scores range from 0 to 30, with a score below 24 indicating cognitive impairment.

During the following six months the study nurse registered all health care utilisation, such as physician visits and hospitalisation with associated main diagnoses, and death dates. Falls with injuries requiring a physician visit or hospital care were considered serious falls, and were used in the prospective analysis.

The sample´s median age of 85 years was chosen to divide the study population into one younger group (<85 years) and one older group (≥85 years). The two age groups were

analysed separately and compared according to the occurrence of serious falls, and use of fall risk drugs.

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 24 (SPSS, Inc. Chicago, IL). Descriptive statistics were used for baseline characteristics. For baseline comparison between the age groups, an independent samples T-test was used for continuous variables, since the mean values were assumed to be normally distributed, and the two-sided Pearson´s chi-square test was used for discrete variables. A p-value of <0.05 was considered statistically significant. A two-sided Pearson's chi-square test was used in the baseline analysis of falls that had occurred. In the prospective analysis of serious falls a two-sided Pearson's chi-square test or Fisher's exact test was used when comparing subjects using or not using the studied drug classes. Binary logistic regression analysis with the Enter method was used to calculate associations between drug use and serious falls in the prospective analysis of the two age groups, with the independent variables analysed separately. These calculations were also performed adjusted for the known fall risk factors: previous falls [24,25] during the last 12 months, anaemia [26] and cognitive impairment [27,28] measured as the occurrence of a dementia diagnosis. To test the robustness of the model we also alternatively defined cognitive impairment as low MMSE score (< 24), or the answer "not orientated" to the DFRI question about orientation. It was not possible to include sex as a covariate in this analysis because of the small number of men in the older age group.

Ethical approval and consent to participate

The SHADES study protocol was approved by the Regional Ethical Review Board, Linköping (no: M150-07 and 2016/67-32). Written informed consent was obtained from all study subjects. For subjects with cognitive impairment who were unable to understand the information, the next of kin were consulted.

Results

Of the 331 study subjects, 234 were women (71%) and 97 were men (29%). The median age at inclusion was 85 years (range 65 to 101 years). The female subjects were significantly ($p < 0.001$) older (mean age 85.6 ± 7.0 years) than the male subjects (mean age 81.8 ± 6.6). The younger group included 164 subjects between 65 and 84 years of age, and the older group included 167 subjects aged 85 years or above. The baseline characteristics of the study population and the two age groups are shown in table 1.

Table 1 Baseline characteristics of the study subjects

Parameter	**All (n=331)**	**Age group**		**P-value Younger group vs older group**
		Younger group (n=164)	**Older group (n=167)**	
Age Range (years)		65-84	85-101	
Age (years) mean (SD)	84.5 (7.1)	78.7 (4.6)	90.1 (3.6)	<0.001 [a]
Women (%)	70.7	62.8	78.4	0.002 [b]
Weight (kg) mean (SD)	67.0 (14.4)	71.2 (14.8)	62.8 (12.6)	<0.001 [a]
Height (cm) mean (SD)	163.4 (9.0)	165.1 (9.1)	161.6 (8.5)	<0.001 [a]
BMI (kg/m²) mean (SD)	25.0 (4.8)	26.1 (5.0)	24.1 (4.3)	<0.001 [a]
MMSE (points) mean (SD)	17.2 (6.4)	17.0 (6.4)	17.5 (6.3)	0.475 [a]
Dementia diagnosis (%)	43.2	49.4	37.1	0.024 [b]
DFRI ≥ 3 points = Fall Risk (%)	92.9	92.0	93.9	0.497 [b]
Systolic blood pressure (mmHg) mean (SD)	135.0 (22.8)	132.2 (21.1)	137.8 (24.1)	0.027 [a]
Diastolic blood pressure (mmHg) mean (SD)	72.8 (11.4)	73.1 (10.9)	72.5 (12.0)	0.639 [a]
Medications in total (SD)	6.9 (3.1)	7.4 (3.2)	6.5 (2.9)	0.008 [a]
Number of psychotropic drugs (SD) *ATC: N05, N06A*	1.2 (1.2)	1.4 (1.2)	1.1 (1.2)	0.015 [a]
Polypharmacy ≥ 10 drugs (%)	22.1	28.0	16,2	0.009 [b]
Psycholeptics, all (%) *ATC: N05* [c]	47.1	48.2	46.1	0.707 [b]
Antipsychotics (%) *ATC: N05A* [d]	13.3	17.1	9.6	0.045 [b]
Benzodiazepines (%) *ATC: N05BA, N05CD*	18.1	21.3	15.0	0.132 [b]
Non-benzodiazepine hypnotics (zopiclone or	24.5	21.3	26.9	0.234 [b]

zolpidem) (%) *ATC: N05CF*				
Antidepressants (%) *ATC: N06A*	47.1	56.7	37.7	0.001 [b]
SSRI (%) *ATC: N06AB*	35.3	39.0	31.7	0.166 [b]
Antihypertensives, all (%) *ATC: C03, C07, C08, C09*	65.0	61.6	68.3	0.203 [b]
Diuretics (%) *ATC: C03*	46.8	43.9	49.7	0.291 [b]
Beta-blockers (%) *ATC: C07*	34.7	36.6	32.9	0.485 [b]
Vasodilators (%) *ATC: C01D, C08C, C08D, C09A, C09C, C09D*	28.4	30.5	26.3	0.404 [b]

[a] Independent samples T-test. [b] Pearson´s chi-square test. [c] Lithium and melatonin excluded [d] Lithium excluded
Abbreviations: SD Standard deviation, BMI Body Mass Index, ATC Anatomical Therapeutic Chemical classification system, SSRI Selective serotonin re-uptake inhibitors.

The study population had on average 6.9 ± 3.1 (0-14) regular drugs. Of all study subjects, 143 (43%) had a dementia diagnosis, but among the individuals tested with the MMSE, 81% had a cognitive impairment (MMSE < 24). A large majority had an increased fall risk as measured by DFRI ≥ 3 (93%, Table 1).

The use of drugs differed between the age groups, with significantly less polypharmacy and use of antidepressants and antipsychotics in the older age group (Table 1). Of the 80 individuals regularly using non-benzodiazepine hypnotics, 67 used zopiclone and 13 zolpidem.

For 62% there was at least one reported fall during the previous year (answer “yes” to DFRI question no. 1). There was a higher occurrence of reported falls during the previous year in the subjects with regular use of non-benzodiazepine hypnotics (p = 0.005) but not for other studied drug classes (Table 2).

Table 2 Subjects with reported falls during the previous 12 months in relation to baseline drug treatment (n=203)

	ATC code	Subjects with falls (%)		P-value Chi-square
		On treatment	Not on treatment	
Polypharmacy ≥ 10 drugs (n=72)		45 (62.5)	158 (61.7)	0.904
Psycholeptics, all (n=154)	*N05* [a]	104 (67.5)	99 (56.9)	0.048
Antipsychotics (n=43)	*N05A* [b]	27 (62.8)	176 (61.8)	0.896
Benzodiazepines (n=59)	*N05BA, N05CD*	37 (62.7)	166 (61.7)	0.886
Non-benzodiazepine hypnotics (n=80)	*N05CF*	60 (75.0)	143 (57.7)	0.005
Antidepressants, all (n=154)	*N06A*	100 (64.9)	103 (59.2)	0.285
SSRI (n=115)	*N06AB*	78(67.8)	125 (58,7)	0.104
Antihypertensives, all (n=213)	*C03, C07, C08, C09*	131 (61.5)	72 (62.6)	0.844
Diuretics (n=153)	*C03*	95 (62.1)	108 (61.7)	0.944
Beta-blockers (n=115)	*C07*	67 (58.3)	136 (63.8)	0.320
Vasodilators (n=94)	*C01D, C08C, C08D, C09A, C09C, C09D*	56 (59.6)	147 (62.8)	0.584

[a] Lithium and melatonin excluded, [b] Lithium excluded.
Abbreviations: ATC Anatomical Therapeutic Chemical classification system, SSRI selective serotonin re-uptake inhibitors.

Over six months, 24 (7.3%) subjects experienced serious falls, 12 in the younger group and 12 in the older group. Those with falls reported the previous year in DFRI had a non-significant tendency towards higher risk for serious falls in the following six months (p=0.094). The occurrence of serious falls in the following six months did not differ significantly for the entire sample when comparing groups of subjects using or not using drugs from different drug classes (Table 3).

Table 3 Subjects with occurrence of serious falls during six months in relation to baseline drug treatment

	ATC code	Subjects with serious falls (%)		P-value
		On treatment	Not on treatment	
Polypharmacy ≥ 10 drugs (n=73)		3 (4.1)	21 (8.1)	0.241 [a]
Psycholeptics, all (n=156)	*N05* [c]	12 (7.7)	12 (6.9)	0.770 [a]
Antipsychotics (n=44)	*N05A* [d]	2 (4.5)	22 (7.7)	0.754 [b]
Benzodiazepines (n=60)	*N05BA, N05CD*	3 (5.0)	21 (7.7)	0.589 [b]
Non-benzodiazepine hypnotics (n=80)	*N05CF*	8 (10.0)	16 (6.4)	0.276 [a]
Antidepressants, all (n=156)	*N06A*	14 (9.0)	10 (5.7)	0.254 [a]

SSRI (n=117)	*N06AB*	11 (9.4)	13 (6.1)	0.265 [a]
Antihypertensives, all (n=215)	*C03, C07, C08, C09*	17 (7.9)	7 (6.0)	0.531 [a]
Diuretics (n=155)	*C03*	13 (8.4)	11 (6.3)	0.454 [a]
Beta-blockers (n=115)	*C07*	8 (7.0)	16 (7.4)	0.880 [a]
Vasodilators (n=94)	*C01D, C08C, C08D, C09A, C09C, C09D*	5 (5.3)	19 (8.0)	0.393 [a]

[a] Pearson´s chi-square test, [b] Fisher´s exact test, [c] Lithium and melatonin excluded [d] Lithium excluded
Abbreviations: ATC Anatomical Therapeutic Chemical classification system, SSRI selective serotonin re-uptake inhibitors.

In the older age group however, there was a significant association between serious falls and regular use of non-benzodiazepine hypnotics (p = 0.017, Odds Ratio = 4.311), but no significant association between serious falls and regular use of the other studied drug classes (Table 4). Among the study subjects treated with non-benzodiazepine hypnotics at baseline, 91% were still on this treatment after six months.

Table 4 Serious fall risk during six months according to age group and baseline drug treatment

Drug class	**Age group**	**p**	**Odds ratio**	**95% CI**
Psycholeptics, all *ATC: N05* [a]	65-84	0.640	0.753	0.229-2.477
	85-101	0.382	1.700	0.517-5.590
Antipsychotics *N05A* [b]	65-84	0.969	0.969	0.200-4.686
	85-101	[c]	[c]	[c]
Benzodiazepines *ATC: N05BA, N05CD*	65-84	0.683	0.721	0.151-3.454
	85-101	0.512	0.496	0.061-4.023
Non-benzodiazepine hypnotics *ATC: N05CF*	65-84	0.278	0.316	0.039-2.531
	85-101	0.017	4.311	1.292-14.377
Antidepressives, all *ATC: N06A*	65-84	0.196	2.429	0.633-9.323
	85-101	0.770	1.195	0.362-3.938
SSRI *ATC: N06AB*	65-84	0.422	1.621	0.499-5.264
	85-101	0.446	1.592	0.481-5.271
Antihypertensives, all *ATC: C03, C07, C08, C09*	65-84	0.329	1.957	0.509-7.521
	85-101	0.902	0.925	0.266-3.217
Diuretics *ATC: C03*	65-84	0.111	2.750	0.794-9.528
	85-101	0.565	0.705	0.215-2.318
Beta-blockers *ATC: C07*	65-84	0.705	1.260	0.382-4.159
	85-101	0.546	0.660	0.171-2.543

Vasodilators *ATC: C01D, C08C, C08D, C09A, C09C, C09D*	65-84	0.669	0.745	0.193-2.876
	85-101	0.559	0.625	0.113-2.558

[a] Lithium and melatonin excluded, [b] Lithium excluded, [c] Too few observations.
Abbreviations: CI Confidence Interval, ATC Anatomical Therapeutic Chemical classification system, SSRI selective serotonin re-uptake inhibitors.

These results did not change when adjusting for the included fall risk factors previous falls, anaemia or cognitive impairment.

Discussion

This study found an association between reported falls during the previous year and regular use of non-benzodiazepine hypnotics. For the older group in the study population, there was an association between regular use of non-benzodiazepine hypnotics and serious falls in the following six months as well. There was no association between reported falls the previous year or serious falls in the following six months, and the other investigated drug classes.

The association between falls and use of non-benzodiazepine hypnotics is important because these compounds are widely used among older people, including individuals living in nursing homes [29]. The results are in accordance with the results from a previous larger study performed in the US that found an elevated risk of hip fractures among nursing home residents using a non-benzodiazepine hypnotic [18]. However, that study population was younger (>50 years, mean age 81) and zopiclone, the most widely used non-benzodiazepine hypnotic in Europe, was not available in the US.

In SHADES, 81 % of the subjects tested with MMSE had a cognitive impairment but only 43 % had a dementia diagnosis, which indicates that dementia is underdiagnosed in this population. The use of psychotropic drugs in SHADES was at the same level as in an earlier report from Swedish nursing homes [29], but lower than in an earlier Swedish study on specialised care units for persons with dementia [30]. However, in SHADES there were considerable differences in psychotropic drug use between the older and younger groups. The

older group were on a polypharmacy regimen (≥ 10 drugs) to a significantly less extent, they used significantly less antidepressants and antipsychotics, and there was a non-significant trend towards lower use of benzodiazepines. Regarding non-benzodiazepine hypnotics the tendency was the opposite, however not significant. A possible explanation for these differences in drug use could be presence of more physical frailty and less psychiatric symptoms in the oldest group. However, another explanation for these differences may be that the medication had been adapted to the higher age group. Polypharmacy and certain types of psychotropic drug use are established risk treatments for older people, a fact that has been highlighted in guidelines [12]. Such an adaptation to established knowledge may also be the reason that this study could not find associations between use of other studied risk drug classes and falls.

Compared to the other studied psychotropic drug classes, non-benzodiazepine hypnotics are newer. They have been considered at least as efficacious as benzodiazepines but with possible safety advantages [31], and are well tolerated by older people [32]. Consequently eszopiclone (in the US) or zopiclone (in Europe) are often recommended as first-line therapies when pharmacological insomnia treatment is needed for older people [12,33,34] and zopiclone is among the drugs that are significantly more used in institutionalised compared to community-dwelling older people in Sweden [29].

More safety concerns on non-benzodiazepine hypnotics related to effects on balance and fracture risk in older people have been raised during the last few years [35,36] and even a possibility of increased mortality has been highlighted [37]. Negative effects from non-benzodiazepine hypnotics on postural stability 4-8 hours after low dose zopiclone or zolpidem intake have been shown in healthy persons aged 64 to 79 years [38,39]. This effect is similar to that with of benzodiazepines, probably because they all act through modulation of the gamma-amino-butyric acid type A ($GABA_A$) receptor complex [39]. Consequently,

non-benzodiazepine hypnotics have now been mentioned as fall risk drugs in the recent versions of Beers Criteria [7,8] and STOPP Criteria [10] published after data was collected for this study.

Some previous studies on non-benzodiazepine hypnotics and fracture risk in older people have found an increased fall risk associated with short-term use or during the first period on a new drug [18,40,41]. However, this study focuses on regular drug use over a longer period and has still found an association with increased fall risk.

In general, there is a lack of studies on fall risk in very old people. However, one study indicates an exceedingly high fall risk in those aged over 90 without considering pharmacological treatment [42]. We found no studies that analysed the use of non-benzodiazepine hypnotics or the effects on stability among the oldest old (≥ 85 years). Consequently, there is need for more knowledge regarding fall risk, with special consideration of pharmacological treatment, in the rapidly growing group of very old people.

Several limitations should be considered in interpreting the findings from the present study. The limited sample of nursing home residents affects the ability to identify all relevant associations, especially when analysing the sample in age groups. The small number of serious falls is an important limitation, and therefore differences in fall risk between drug-users and non-users need to be confirmed in larger studies. There may have been a selection bias in the nursing homes studied, since they were not randomly selected but were chosen by convenience from three geographical areas. Nursing homes showing interest were chosen for the study because the study was dependent on stable conditions to facilitate repeated measurements. The research group judged that the nursing homes included in this sample were typical of Sweden, and the placement of the nursing homes in three different municipalities increases the chance that they are representative [19]. However, we cannot

exclude the possibility that there may have been an increased awareness about inappropriate drug use in the included nursing homes. An important limitation is that the data were collected in the period 2008-2011, and traditions in drug use and health status of older people living in nursing homes may have changed during the last few years. The baseline registration of occurred falls during the last 12 months is based on the answer from the nursing home staff to a question about whether or not the person had fallen and not on a formal registration. Orthostatic blood pressure is a relevant fall risk factor to consider but we do not have such data. The study did not consider well-being or quality of life in relation to adequate drug use. Moreover, we were not able to investigate dose-response relationships due to the small overall sample size, and data about drugs taken as needed were not registered. Finally, we neither knew the start dates for different drugs, nor were we able to confirm that a subject was still on the same medication when a serious fall occurred up to six months later. However, there were few changes in the treatment with non-benzodiazepine hypnotics over the study period of six months.

Conclusions

In this study a great majority of nursing home residents had increased fall risk. Regular use of non-benzodiazepine hypnotics was associated with a history of falls, and prospectively with serious falls in the older age group. These findings indicate a need for increased caution regarding regular non-benzodiazepine hypnotic therapy for insomnia in older people living in nursing homes, especially among the oldest. The results from this study need to be confirmed in larger studies, but they highlight a need for more research on the use of non-benzodiazepine hypnotics and their association with falls in older people, especially in the oldest age group.

Notes

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Compliance with ethical standards

Conflict of interests

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

Statement of human rights

The SHADES study protocol was approved by the Regional Ethical Review Board, Linköping (no: M150-07 and 2016/67-32).

Informed consent

Written informed consent was obtained from all study subjects. For subjects with cognitive impairment who were unable to understand the information, the next of kin were consulted.

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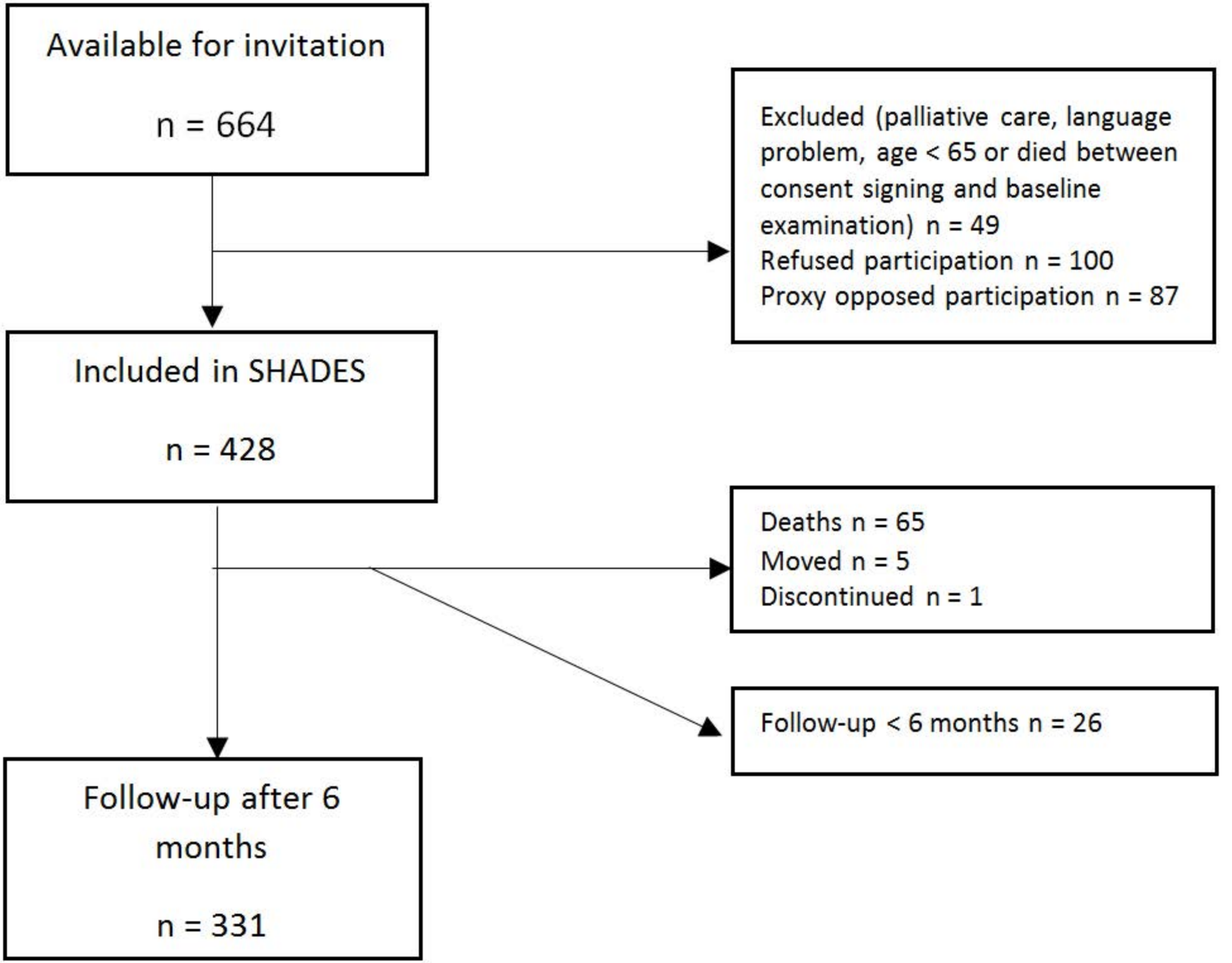
Available for invitation
n = 664
Excluded (palliative care, language problem, age < 65 or died between consent signing and baseline examination) n = 49
Refused participation n = 100
Proxy opposed participation n = 87
Included in SHADES
n = 428
Deaths n = 65
Moved n = 5
Discontinued n = 1
Follow-up < 6 months n = 26
Follow-up after 6 months
n = 331