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Mortality and health-related quality of life in older adults with long-term use of opioids, z-hypnotics or benzodiazepines: a prospective observational study at 5 years follow-up

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ABSTRACT

Objectives Disease and medication use in older age is a consequence of age-related declining health. Multimorbidity followed by polypharmacy is common. Central nervous system depressing (CNSD) drugs such as opioids, benzodiazepines and z-hypnotics are not recommended for long-term use in older adults but are in use by many. We aimed to assess mortality and change in health-related quality of life (HRQoL) in older adults with long-term use of CNSDs.

Method A prospective observational study was conducted at Akershus University Hospital, Norway, 2017–2019, with follow-up in 2021–2022, including 246 participants aged 65–90. At 5-year follow-up, 78 (32%) participants had passed away. Mortality data were collected from patient electronic health records. Of the surviving 168 (68%), we collected further follow-up data from 38 (16%) participants. Follow-up included demographic and clinical data. The EuroQuol Group EQ-5D-5L questionnaire was used to measure HRQoL. Analysis include Cox regression model for survival data and linear mixed model for change in HRQoL over time.

Results At follow-up, 78 (31.7%) were deceased. Mean survival time was 3.3 years. Total time for survival data was 4.7 years. Mortality was higher among participants with long-term use of CNSD (HR 1.9 95% CI (1.2 to 3.2), p=0.01). The multivariable analysis found being older (HR 1.1 95% CI (1.0 to 1.1), p=0.020) and male sex (HR 2.1 95% CI (1.2 to 3.5), p=0.008) to be associated with increased risk of mortality. According to the linear mixed model (n=38), there was no significant difference between surviving users and non-users in change in HRQoL EQ-5D-5L index from baseline to follow-up.

Conclusion Mortality was higher for long-term users of CNSDs at 5-year follow-up. Being older and male sex were associated with mortality. Among survivors, there was no significant difference between the groups in change of HRQoL over time.

Trial registration number NCT03162081; 22 May 2017.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study explores direction and strength of relationship between use of central nervous system depressing medications and mortality in older adults.
⇒ The main strength of this study is using clinical and participant-reported data collected directly from the subjects. This is particularly so since register studies is the prevalent method for investigating long-term use of CNSDs in this population.
⇒ The relatively small original sample and the attrition of participants at follow-up may limit the generalisability of the findings in the study.

INTRODUCTION

Health issues affecting quality of life include pain, sleep difficulties and anxiety. Pharmacological options for treatment include opioids, z-hypnotics (zopiclone and zolpidem) and benzodiazepines. Although international and Norwegian clinical guidelines discourage long-term (≥4 weeks) use of such medications,[1 2] it is well documented that a considerable proportion of the older adult population is taking such drugs on a regular basis.[3–10] In Norway, prevalence of long-term use for older adults is reported to be approximately 17% for opioids[10] and 25% for z-hypnotics and benzodiazepines.[6] Among older adults, these medications are associated with severe side effects such as tolerance, addiction, falls, fractures and reduced cognitive function. These are all factors that are known to contribute to considerable costs to the healthcare system.[6 11–14] Although these medications are indicated to improve health-related quality of life (HRQoL), research suggests that long-term use is associated with poorer HRQoL.[15–17] Finally, these medications are, either on their own or in combination with each other, associated with increased risk of all-cause mortality.[18–25]

As both international and Norwegian clinical guidelines discourage long-term use of these drugs,[1 2] in 2017–2018, we conducted a study at Akershus University Hospital, Norway investigating use of these medications among hospitalised older adults. For the purpose of the study, and based on their inhibitory effects on the central nervous system (CNS), the medications were collectively referred to as CNS depressing medications (CNSDs). We found that among 246 hospital-recruited older adults, 40% had long-term (≥4 weeks) use of CNSDs and that a range of factors including sociodemographic, reduced cognitive function, pain and disease burden were associated with long-term use. Our preliminary study at 2-year follow-up found that age, cognitive function and CNSD use were associated with mortality.[5 26–29] In the present study, performed in 2021–2022, we followed-up on the cross-sectional study with the aim to investigate mortality, and change in HRQoL over time in this group of older adults with and without long-term use of CNSDs.

METHOD

Study design and setting

This prospective observational study was conducted at Akershus University Hospital (Lørenskog, Norway). Data were collected at two time points. Two-hundred and forty-six participants aged ≥65 were recruited during spring 2017 to autumn 2018. Of these, 38 cases and matched controls were followed up autumn 2021 to winter 2022. Characteristics of the baseline population (2017–2019) and relevant outcomes have been published elsewhere.[5 15 26–28 30 31]

Study participants

At the primary data collection point, older adults aged ≥65 were consecutively recruited from three departments at Akershus University Hospital; the geriatric, general internal medicine and neurology departments. For the primary data collection, 665 participants were approached and a final of 246 participants were included. Full information on the primary data collection and recruitment process, including participant flowchart, has been previously published elsewhere.[5] For the secondary data collection, we had consent to recontact and follow-up 129 participants. Of these, we were able to recruit 19 participants who had long-term use of CNSDs at baseline and 19 non-users matched on age and sex. Exclusion criteria for both collection points included mini-mental state examination (MMSE) score ≤21,[32] pre-existing diagnosis including moderate to severe depression, stroke, dementia, psychotic disorders, serious visual or hearing impairment and insufficient language skills to complete an interview and questionnaires in Norwegian.[5] For full participation chart, see figure 1. Data on mortality were collected from electronic health records and predefined censoring date was 1 January 2022. Due to restrictions caused by the COVID-19 pandemic regulations, we were not able to follow-up all the 66 non-matched non-users within the timeframe that we had.

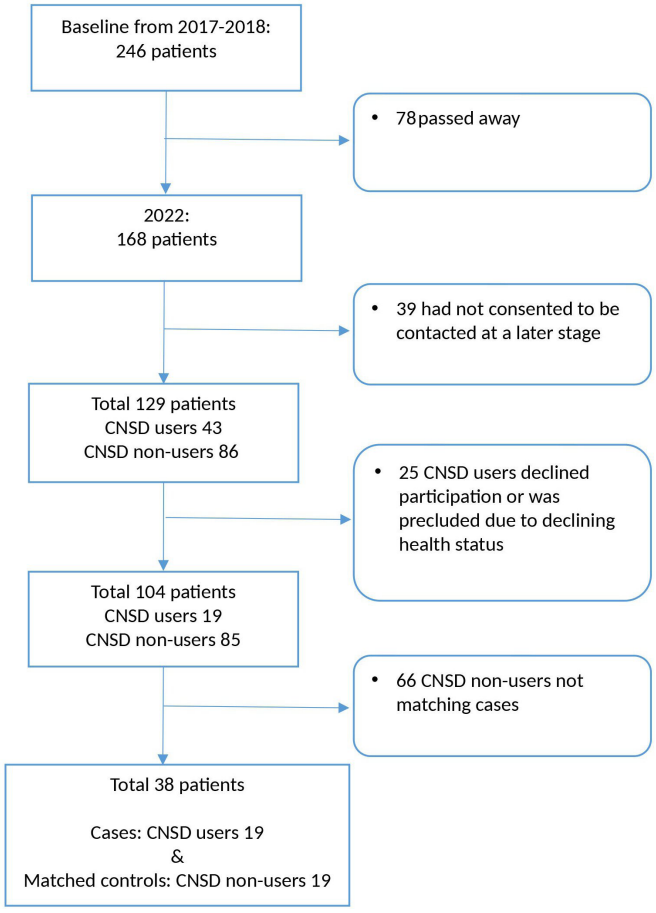

Figure 1 Study participation flowchart. CNSD, central nervous system depressing.

Data collection

Data were collected through extraction from patient electronic health records, self-conducted patient questionnaires as well as investigator-conducted special tests by three accordingly trained study investigators (TBS, MTB and CL) during autumn of 2021 to winter of 2022. Variables included for analysis were age, sex, level of education, cognitive function, anxiety/depression, loneliness, pain, quality of life, disease burden, CNSD use and mortality rate. The following instruments were used.

The Mini-Mental State Examination

The MMSE instrument measures cognitive function. It consists of 11 items and the test score range from 0 to 30, where a score of<25 is considered cognitive impairment.[33]

The Cumulative Illness Rating Score—Geriatrics

The Cumulative Illness Rating Score—Geriatrics (CIRS-G) is a 56-point scale that rates severity of disease in major body organ systems. The higher the score, the more severe the burden of disease.[34]

The six-item De Jong Giervald Loneliness Scale

The six-item De Jong Giervald Loneliness Scale measures the two items social and emotional loneliness. It is scored from 0 to 6 where zero indicates no loneliness.[35]

The Hospital Anxiety and Depression scale

The Hospital Anxiety and Depression Scale (HADS) measures the two subdimensions anxiety and depression in a 14-item scale where each item is scored from 0 to 3. It is scored from 0 to 21 where a higher score indicates more severe symptoms.[36]

The EuroQol Group EQ-5D-5L

The EuroQol Group EQ-5D-5L is a five-dimensional and five-layered scale designed to measure HRQoL. It consists of the five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each scored from 1 to 5. These scores are combined into an index ranging from 0 to 1 where one implies full health. The instrument also contains the 101-point graphic rating scale where 0 is worst imaginable health and 100 is best imaginable health.[37] In this study, we used the van Hout *et al* 2021 EQ-5D-3L to EQ-5D-5L crosswalk value sets to obtain EQ-5D index.[38]

Visual analogue scale for pain intensity

Visual analogue scale (VAS) for pain intensity is a scale where one is asked to put a mark on a 100 mm blank line where 'no pain' is indicated on the left as 0 and 'worst possible pain' is indicated on the right (100). It is score from 0 to 100.[39]

Statistical analysis

The demographic and clinical participant characteristics are presented as means with (SDs) or frequencies with percentages for the entire sample and stratified by groups of baseline status as CNSD user or CNSD non-user. Independent samples t-test and Pearson's χ^2 test were used to compare the two groups on continuous and categorical variables, respectively. Survival and mortality data are presented as mean survival time, between-groups mortality rate with 95% CIs and illustrated by Kaplan-Meier survival plots. HR for mortality was assessed using univariate and multivariable Cox regression analysis. The following variables were included; sex, age, education, MMSE, CIRS-G, HADS, loneliness, VAS pain intensity and use of CNSDs. Analysis was performed on cases with no missing values on explanatory variables. Participants included and excluded in the Cox analysis were compared using independent samples t-test and Pearson's χ^2 test. Proportional hazard assumption was assessed by global tests. Potential non-linear associations were assessed by including higher order variables into the model. Schoenfeld residuals were inspected graphically for selected variables. Linear mixed models with random intercepts for participants and fixed effects for time, group and the interaction between the two were estimated to compare change in reported quality of life over time between CNSD users and non-users. If not significant, interaction was removed from the model. All between-group differences were regarded as statistically significant if p<0.05. Statistical analysis was performed using IBM SPSS Statistics for Windows ((V.28.0) IBM released 2021. Armonk, New York) and StataCorp. 2021. Stata Statistical Software: Release V.17. College Station, Texas: StataCorp LLC.

Patient and public involvement statement

The Health Services Research Unit User Advisory Board at Akershus University Hospital has provided advice and recommendations through patient and public involvement throughout all stages of the research project. They have throughout been informed of study results and publications.

RESULTS

Participants

Baseline demographics included 246 older adults with a mean age of 76.6 (SD 6.6) years, whereof 55.7% were women. Mortality data were collected on all 246 participants who were recruited at baseline. Among those, 78 (32%) were registered as passed away by censoring date 1 January 2022. Of the remaining 168, 129 participants had given consent to be contacted for follow-up. Among these, there were 43 participants who were registered as CNSD users at baseline. Of these, 19 were recruited for follow-up. Another 19 participants in the CNSD non-user group were further recruited as controls, matched on age and sex (total n=38). Thus, the follow-up included 38 participants with mean age of 77.8 (6.0), whereof 78.9% were women. Demographic information is presented in table 1 and full overview of the participation flow-chart is presented in figure 1.

Survival analysis and Cox-regression for hazard of mortality

Total time for collection of survival data was 243.3 weeks (4.7 years). Mean survival time was 169.8 weeks (3.3 years) for all participants. The mortality rate was higher among CNSD users compared with non-users (HR 1.9 95% CI (1.2 to 3.2), p=0.01). Kaplan-Meier survival plot comparing CNSD-users versus non-users is presented in figure 2A (p=0.001 for log-rank test). For illustration, we also present a Kaplan-Meier survival plot comparing all CNSD medication groups (figure 2B).

Complete case analysis was done, excluding 54 participants in the Cox regression analysis. Comparing the excluded (n=54) with the included (n=192) participants, the cognitive score (MMSE) was significant lower among the excluded participants (p=0.005). Level of education was also significantly lower in the excluded group (p=0.025). There was no significant difference in sex, age, CIRS-G, HADS, loneliness, pain VAS and long-term use of CNSDs between the participants excluded and included in the Cox regression analysis.

The bivariate Cox regression model (table 2) shows that the following covariates were statistically significantly associated with increased mortality; being a user of CNSDs

Table 1 Profile of participants on baseline and follow-up stratified by groups of CNSD-use and non-use

	Baseline				Follow-up with baseline status as non-user or user			
Covariates	**Total (n=246)**	**Non-user (n=146)**	**User (n=100)**	**P value**	**Total (n=38)**	**Non-user (n=19)**	**User (n=19)**	**P value**
Sex female (%)	137 (55.7)	71 (48.6)	66 (66.0)	**0.007***	30 (78.9)	15 (78.9)	15 (78.9)	1.000*
Age mean (SD)	76.6 (6.6)	75.3 (6.4)	78.5 (6.5)	**<0.001†**	77.8 (6.0)	77.1 (5.8)	78.6 (6.2)	0.453†
Education, years (%)	(n=236)				(n=37)			
Basic≤10	47 (19.9)	17 (12.2)	30 (30.9)	**0.002***	4 (10.5)	2 (10.5)	2 (11.1)	0.868*
Secondary 11–13	99 (41.9)	65 (46.8)	34 (35.1)		16 (42.1)	9 (47.4)	7 (38.9)	
Higher≥14	90 (38.1)	57 (41.0)	33 (34.0)		17 (44.7)	8 (42.1)	9 (50.0)	
MMSE	(n=215)							
Mean (SD)	25.4 (2.7)	25.7 (2.7)	24.8 (2.6)	**0.015†**	28.8 (1.5)	29.1 (1.0)	28.5 (1.9)	0.252†
CIRS-G mean (SD)	5.9 (2.8)	4.7 (2.1)	7.7 (2.7)	**<0.001†**	7.7 (3.3)	6.2 (2.8)	9.3 (3.1)	**0.003†**
Loneliness mean (SD)	(N=234)							
	1.5 (1.6)	1.2 (1.5)	2.0 (1.8)	**<0.001†**	1.8 (1.7)	1.5 (1.7)	2.2 (1.6)	0.253†
HADS, total mean (SD)	(n=229) 8.7 (6.0)	7.7 (5.3)	10.1 (6.7)	**0.004†**	8.7 (5.3)	8.1 (6.5)	9.3 (3.8)	0.509†
EQ-5D-5L	(n=239)							
Index mean (SD)	0.62 (0.3)	0.69 (0.3)	0.51 (0.3)	**<0.001†**	0.63 (0.2)	0.68 (0.3)	0.58 (0.2)	0.205†
Median	0.69	0.77	0.57	–	0.68	0.73	0.59	–
(min;max)	(–0.3;1.0)	(–0.3;1.0)	(–0.3;1.0)		(–0.02;1.0)	(–0.02;1.0)	(–0.01;1.0)	
EQ-5D-5L								
VAS	57.3 (21.6)	62.4 (23.0)	49.7(17.0)	**<0.001†**	62.5 (20.8)	66.3 (23.0)	58.7 (18.3)	0.269†
Mean (SD)	60.0	63.5	50.0	–	60.0	65.0	51.0	–
Median (min;max)	(0.0;100.0)	(0.0;100.0)	(0.0;80.0)		(29.0;95.0)	(29.0;95.0)	(30.0;90.0)	
Pain	(n=228)							
VAS mean (SD)	25.0 (28.1)	18.1 (24.2)	35.2(30.4)	**<0.001†**	28.9 (28.4)	21.6 (26.0)	36.3 (29.5)	0.112†
Pain VAS median (min; max)	10.5 (0.0;97.0)	7.0 (0.0;91.0)	29.5 (0.0;97.0)	–	19.5 (0.0;94.0)	9.0 (0.0;94.0)	27.0 (2.0;90.0)	–

The numbers in bold are statistically significant their p-value is below 0.05
*x^2 test.
†Independent samples t-test.
CIRS-G, cumulative illness rating score—geriatrics; CNSD, central nervous system depressing; EQ-5D-5L, The EuroQol Group EQ-5D-5l instrument for measuring HRQoL; HADS, Hospital Anxiety and Depression Scale; MMSE, mini-mental state examination; VAS, visual analogue scale.

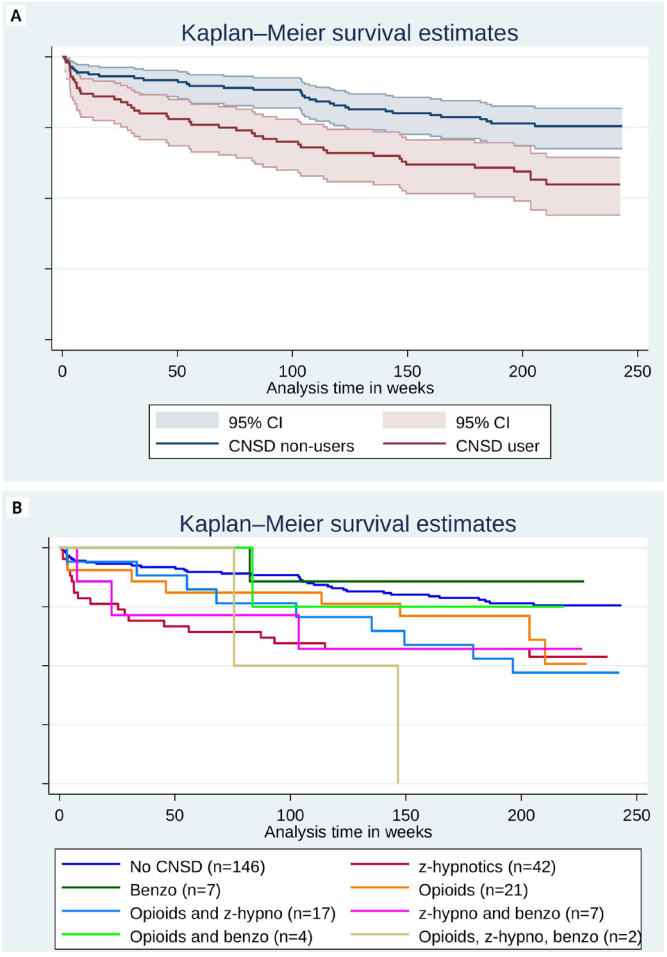

Figure 2 (A) Survival estimates between CNSD users (n=100) and non-users (n=146). (B) Survival estimates for all non-CNSD users and all CNSD medication groups (n=246). CNSD, central nervous system depressing.

(HR 1.9 95% CI (1.2 to 3.2), p=0.010), higher age (HR 1.1 95% CI (1.0 to 1.1), p<0.001), lower cognitive function measured in MMSE (HR 0.9 95% CI (0.8 to 0.9), p=0.001) and more disease burden measured in CIRS-G (HR 1.2 95% CI (1.1 to 1.3), p<0.001). In the multivariable model, higher age (HR 1.1 95% CI (1.0 to 1.1), p=0.020) and male sex (HR 2.1 95% CI (1.2 to 3.5), p=0.008) were associated with higher risk of mortality (see table 2 for full results). The assumptions of multivariable Cox regression model were met.

HRQoL in CNSD users and non-users (n=38)

There was no statistically significant difference in mean EQ-5D index at baseline between CNSD-users (0.49 (SD 0.2)) and non-users (0.63 (SD 0.3)) and EQ VAS for CNSD-users (52.3 (SD 18.5)) and non-users (63.7 (SD 26.0)). Seven of the 38 participants had their status of being a CNSD- user or not changed at follow-up. Three participants changed from being a non-user to being a user and four participants changed from user to non-user, leaving a total of 18 participants in the CNSD-user group and 20 participants in the non-user group at follow-up. However, all results were based on analysis where the participants were dichotomised on their baseline status of CNSD use. The EQ-5D-5L dimensions; mobility, self-care, usual activities pain/discomfort and anxiety/depression and the five layers; no, slight, moderate, severe and unable/extreme are illustrated in figure 3A,B. Figure 3A shows percentages of all patients at baseline dichotomised as non-users and users (n=239 (missing n=7)) and figure 3B illustrates percentages of the participants who were followed-up (n=38) at both time points.

There was no significant interaction between time and status of being a CNSD user in either of our models, implying no difference between users and non-users

Table 2 Bivariate and multivariable Cox regression assessing hazard for mortality (n=192)

Covariate	Bivariate Hazard ratio (95% CI)	P value	Multivariable model Hazard ratio (95% CI)	P value
Sex				
Male	1.6 (1.0 to 2.6)	0.067	2.1 (1.2 to 3.5)	**0.008**
Age	1.1 (1.0 to 1.1)	**<0.001**	1.1 (1.0 to 1.1)	**0.020**
Education (missing 10)				
Basic≤10 years	1.2 (0.6 to 2.4)	0.529	1.0 (0.5 to 2.1)	0.987
Secondary 11–13 years(ref)				
Higher≥14 years	0.8 (0.4 to 1.4)	0.415	1.0 (0.6 to 1.8)	0.971
MMSE (missing 31)	0.9 (0.8 to 0.9)	**0.001**	0.9 (0.8 to 1.0)	0.053
CIRS-G	1.2 (1.1 to 1.3)	**<0.001**	1.1 (1.0 to 1.2)	0.071
HADS total (missing 17)	1.0 (1.0 to 1.1)	0.351	1.0 (1.0 to 1.0)	0.499
Loneliness (missing 12)	1.0 (0.9 to 1.2)	0.683	1.0 (1.0 to 1.2)	0.727
Pain VAS (missing 18)	1.0 (1.0 to 1.0)	0.288	1.0 (1.0 to 1.0)	0.125
CNSD use	1.9 (1.2 to 3.2)	**0.010**	1.6 (0.9 to 3.0)	0.143

CIRS-G, cumulative illness rating score –geriatrics; HADS, Hospital Anxiety and Depression Scale; MMSE, mini-mental state examination; VAS, visual analogue scale for pain intensity.

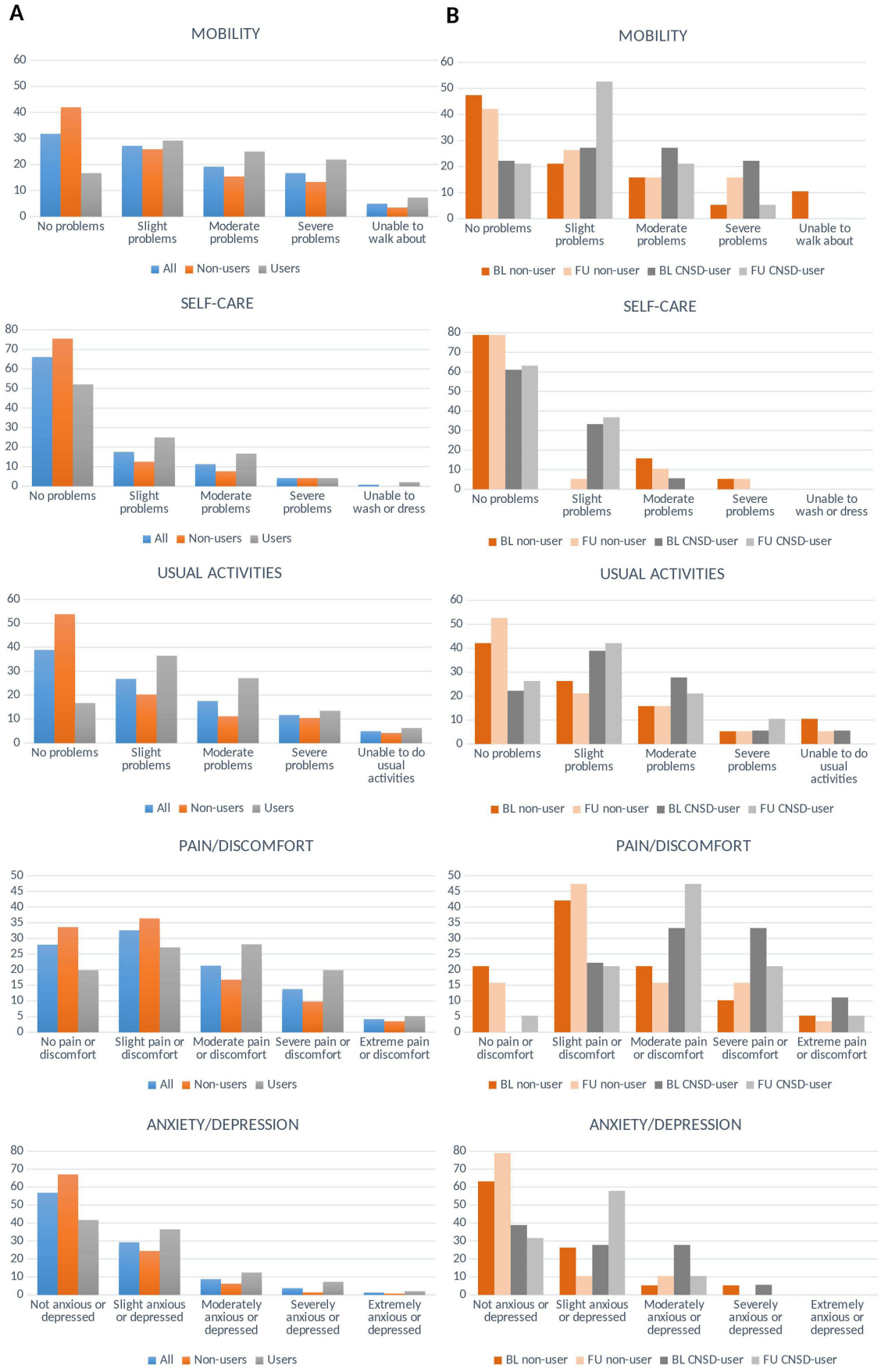

Figure 3 (A) Descriptive presentation of five items and five levels of all (n=239) patients at baseline. (B) Descriptive presentation of five items and five levels of (n=38) patients at baseline and follow-up. CNSD, central nervous system depressing. BL - baseline.

regarding change from baseline to follow-up. Hence, the interaction was removed from the model. In the linear mixed model without interaction, we found a significant improvement in EQ-5D index for all participants over time with regression coefficient (RC) 0.1 95% CI (0.0 to 0.1) (p=0.041), while CNSD-users were found to have non-significantly lower quality of life than non-users (RC—0.1 95% CI (−0.3 to 0.0), p=0.145). We had similar findings for the EQ VAS where there was a non-significant improvement over time among all participants (RC 3.5 95% CI (−4.2 to 11.3), p=0.372) with no difference between users and non-users (non-significant interaction), while the CNSD-users had a non-significant reduction in EQ VAS (RC −9.1 95% CI (−20.0 to 1.9), p=0.105).

Demographic information on participants who were deceased or excluded

For completeness, the baseline demographic data of those who passed away and those who were not included in the follow-up are added in online supplemental appendix 1. The CNSD users were significantly older, had greater burden of disease, greater pain intensity and lower HRQoL than non-users in these two cohorts. In online supplemental appendix 2, we present demographic information on the follow-up cohort dichotomised by their current status as CNSD-user and non-user. Those with status as CNSD-users at follow-up had significantly greater burden of disease, lower HRQoL and greater pain intensity than non-users. In online supplemental appendix 3, we compare demographic status at baseline between those who passed away and those that survived. Among the ones that passed away, there were significantly more CNSD-users, men, they were older and had greater burden of disease. There was, however, no significant difference in HRQoL at baseline.

DISCUSSION

In this prospective observational study, we investigated mortality and change in HRQoL of 246 Norwegian older adults with and without long-term use of CNSD medications at approximately 5-year follow-up. We found a significantly higher mortality rate that was almost two times higher in CNSD users compared with non-users. Adjusting for relevant factors, we found that higher age and male sex were associated with higher risk for mortality in this group of older adults. Among survivors, there was an overall improvement, but no significant difference between CNSD-users and non-users in change in HRQoL from baseline to follow-up (subsample n=38).

Mortality and use of opioids, z-hypnotics and benzodiazepines

Long-term use, or use for ≥4 weeks, of potentially addictive medications such as opioids, z-hypnotics and benzodiazepines should be avoided if possible.[1 2] This is even more important for the older patient, as these medications are associated with severe side effects, including falls, fractures and reduced cognitive function in this population.[6 11–14] We found a mortality rate that was almost two times higher among participants with a history of long-term use of these medications. This agrees with the findings of other reported studies, which have found similar results with increased risk of all-cause mortality.[18–22]

In the bivariate Cox regression, we found that higher age, reduced cognitive function and disease burden were significantly associated along with being a CNSD user. Disease burden, reduced cognitive function and CNSD use are all factors that may be an expression of disease/reduction in health, but in the multivariable analysis, adjusting for relevant covariates, we found only higher age and male sex to be factors associated with higher risk of mortality. Male sex is generally associated with increased mortality,[40] and it appears that in this group of participants, age and male sex are more relevant factors towards risk of mortality than both disease burden and medication use. These findings were perhaps surprisingly so, as there was a higher proportion of female sex among CNSD users together with higher mortality rate among CNSD users. However, Crimmins *et al* argue that a difference in life expectancy also varies with different dimensions of health in older age.[40] Both disease, mortality and being a long-term user of CNSDs might be factors associated with health-seeking behaviours that are more observed in women than in men, or the other way around. This might account for some of the explanation in variation in both CNSD-use and mortality between the sexes found in our study.

HRQoL and use of opioids, z-hypnotics and benzodiazepines

The three medication groups investigated in this study are pharmacological options indicated to alleviate pain, reduce anxiety and improve sleep. While these may be symptoms of disease, they are also factors that have major impact on experienced HRQoL. Although there is research suggesting that long-term use of CNSDs is associated with reported poorer HRQoL,[15–17] it is also reasonable to argue that pharmacological options that address symptoms potentially associated with reduced HRQoL should, in fact, improve it. The EuroQuol Group EQ-5D-5L instruments measure HRQoL through the five dimensions, mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[37] Among the 246 participants recruited at baseline, there was a significantly lower HRQoL among the CNSD-users compared with non-users but is difficult to ascertain if, and to what direction and degree, the CNSDs impact the symptoms associated with HRQoL.

In our follow-up study including 38 users and non-users, we investigated what happened to HRQoL over time in the two groups. We found that there was an overall significant improvement in EQ-5D index in both groups from baseline to follow-up. The CNSD users scored lower on HRQoL at follow-up, though not significantly differently compared with the non-users. This was perhaps not surprising as there was no statistically significant difference in reported HRQoL among the 38 follow-up

participants at baseline. In addition, as we were only able to follow-up on a relatively small group, statistical power may be a problem. Finally, 78 (32%) participants having passed away and with a further selected group available for follow-up, it is reasonable to argue that the group of participants who were followed-up were a selected group of participants, and not a direct reflection the full original cohort recruited at baseline.

Comparing the overall EQ-5D index and EQ VAS with the Norwegian population norm,[41] one finds that among the age group 70–79, the mean EQ-5D index is 0.781 and the EQ VAS is 78.4. That is substantially higher than both mean EQ-5D index and EQ VAS at baseline in our study. We suggest that the reason for this difference is the setting where the study participants were recruited. While the population norm was collected through postal surveys of the general population, our participants were originally recruited during a hospital admission. Acute disease during a hospital admission may impact individual responses in the EQ-5D instrument. This, in turn, may also be part of the reason why we found an overall improvement in HRQoL from baseline to follow-up.

With regards to the EQ-5D instrument for measuring HRQoL, the instrument may have some shortcomings in this current setting. Pain/discomfort and anxiety/depression are the two dimensions in the EQ-5D questionnaire that are greatest connected to the three medication groups that we investigated. But the medication type that was used by the largest proportion of participants in our study was z-hypnotics,[5] which are used to treat sleep difficulties. Although sleep quality is a major component of HRQoL, the EuroQuol Group EQ-5D instrument does not measure sleep quality. As a result, the status of being a long-term user of CNSDs may be linked to sleep difficulties, and with the instrument used in this setting, it is difficult to discern if it has an impact on HRQoL.

What comes first; disease or medication use?

Medication use in general comes because of symptoms of disease. But it is well documented that medication groups such as the opioids, z-hypnotics, benzodiazepines that are known to have a range of potentially severe side effects, sometimes cause injuries and disease[6 11–14] as well as increased risk of mortality.[18–22] This is particularly so in older adults and with long-term use of such medications.[1 2] Pain, sleep disturbance and anxiety may be symptoms of a range of diseases. They may also be symptoms of side effects from medication use.[42–46] In addition to this, the symptoms of chronic pain,[47–50] sleep difficulties[51] and anxiety[52 53] are all associated with increased risk of mortality. It is, therefore, worth noting the complexity of the direction of associations between symptoms, disease, mortality and medication use. In this study, we found that older age and male sex were the only factors associated with mortality at 5-year follow-up. However, observing all the analysis on demographic profile in this study (table 1 and appendices 1–3), the long-term CNSD users do suffer from greater disease burden with higher CIRS-G score, more cognitive decline, higher pain intensity and lower HRQoL when compared with non-users. Prescription routines should continue to be treated with great care among older adults. As it has been argued by others, symptoms that interfere with daily life activities are associated with greater risk of mortality,[49] non-pharmacological interventions aimed at improving lifestyle factors and conservative options for management of symptoms may be of great benefit also for the older adult.[52 54 55]

Strengths and limitations

In this study, we have investigated mortality, HRQoL and use of potentially addictive medications in older adults. We have obtained clinical data from the patients through patient consultations and not through register studies as often is seen in research in older adults. The main strength of this study is exploring directions of relationships between disease and medication use by using patient-reported data.

As compared with included cases, participants excluded from the Cox regression analysis had statistically significantly lower cognitive function and lower education. Both covariates are suggested to be individually associated with mortality.[56–58] The exclusion of these cases might have caused an underestimation of the effect.

Due to constraints on time and resources, we were not able to do a follow-up of all the surviving participants, which left us to exclude 66 participants who were not matching cases. A large proportion of participants had declined consent for recontact and another proportion declined follow-up due to declining health. It would have been a great advantage to this study to have information from all participants included at baseline both to observe possible change in medication use, burden of disease and HRQoL.

The small original sample and the attrition of participants at follow-up limits the generalisability of the findings in this study. The large proportion of deceased participants left us with a further reduced cohort available for follow-up and, therefore, possible loss of statistical power. There was a greater proportion of CNSD users in the deceased group. In addition, there was greater burden of disease and lower HRQoL among the long-term CNSD users in both the groups who were not included for follow-up and the group of deceased participants. The loss of participants through death and reduction in health left us with a selected cohort that in turn possibly affected the results obtained in the follow-up analysis. Adding to this, as we conducted the matching of cases based on the same parameters that were found to be associated with mortality (ie, age and sex), this may further have affected the results in the follow-up analysis.

Conclusion

At approximately 5-year follow-up, mortality rate was higher for long-term users of CNSDs. Further analysis found that male sex and higher age were associated with elevated risk of mortality, while long-term use of CNSDs

was not associated. Furthermore, both the CNSD-users and the non-users who were included for follow-up had an improvement in HRQoL over time and while the CNSD-users had lower HRQoL at follow-up, this was not significantly different from the non-users. Regardless of this, all the demographic follow-up data support the baseline data indicating greater disease burden and lower HRQoL among CNSD users and care should be taken when prescribing these medications to older adults.

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Contributors CL together with MTB, TGS and JSB designed the follow-up study based on the original cross-sectional study designed by CL, TGS, SC, RG and JSB. MTB, TBS, TGS, SC, RG, JSB and CL all contributed in the data collection. MTB and JSB performed the statistical analyses. MTB drafted the main manuscript. CL was the project managerand acts as guarantor for the content provided in this manuscript. All co-authors have revised and approved the entire content of this manuscript and approved its submission.

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Competing interests CL has participated on an advisory board and received payment for lectures arranged by Abbvie Pharma AS, Novartis AS, Lundbeck AS and Roche AS, Norway. He has also received research sponsorship from Abbvie Pharma. The other authors state no conflict of interest.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Regional Committees for Medical and Health Research Ethics [2016/2289]. Participants gave informed consent to participate in the study before taking part.

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