

This is a self-archived version of an original article. This version may differ from the original in pagination and typographic details.

Author(s): Mikkola, Tuija M.; Mänty, Minna; Kautiainen, Hannu; von Bonsdorff, Mikaela B.; Koponen, Hannu; Kröger, Teppo; Eriksson, Johan G.

Title: Use of prescription benzodiazepines and related drugs in family caregivers : a nation-wide register-based study

Year: 2022

Version: Published version

Copyright: © The Author(s) 2022. Published by Oxford University Press on behalf of the British

Rights: CC BY-NC 4.0

Rights url: <https://creativecommons.org/licenses/by-nc/4.0/>

Please cite the original version:

Mikkola, T. M., Mänty, M., Kautiainen, H., von Bonsdorff, M. B., Koponen, H., Kröger, T., & Eriksson, J. G. (2022). Use of prescription benzodiazepines and related drugs in family caregivers : a nation-wide register-based study. *Age and ageing*, 51(12), Article afac279.
<https://doi.org/10.1093/ageing/afac279>

SHORT REPORT

Use of prescription benzodiazepines and related drugs in family caregivers: a nation-wide register-based study

TUIJA M. MIKKOLA^{1,2}, MINNA MÄNTY^{3,4}, HANNU KAUTIAINEN^{1,5}, MIKAELA B. VON BONSDORFF^{1,6}, HANNU KOPONEN⁷, TEPPU KRÖGER^{8,9}, JOHAN G. ERIKSSON^{1,10,11,12}

¹Folkhälsan Research Center, Helsinki, Finland

²Clinicum, Faculty of Medicine, University of Helsinki, Helsinki, Finland

³Unit of Strategy and Research, City of Vantaa, Vantaa, Finland

⁴Department of Public Health, University of Helsinki, Helsinki, Finland

⁵Primary Health Care Unit, Kuopio University Hospital, Kuopio, Finland

⁶Gerontology Research Centre and Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

⁷Department of Psychiatry, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

⁸Department of Social Sciences and Philosophy, University of Jyväskylä, Jyväskylä, Finland

⁹Centre for Care Research West, Western Norway University of Applied Sciences, Bergen, Norway

¹⁰Singapore Institute for Clinical Sciences, Agency for Science, Technology, and Research, Singapore, Singapore

¹¹Department of Obstetrics & Gynaecology and Human Potential Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

¹²Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland

Address correspondence to: Tuija M. Mikkola, Folkhälsan Research Center, PO Box 21 I, 00251 Helsinki, Finland.

Email: tuija.mikkola@folkhalsan.fi

Abstract

Background: objective indicators of sleep and mental health problems in family caregivers have rarely been reported.

Objective: to study the use of prescription benzodiazepines and related drugs (BZDRD) in Finnish family caregivers and matched controls.

Design: prospective follow-up in 2012–17.

Setting: nationwide register-linkage study.

Subjects: all individuals who received family caregiver's allowance in Finland in 2012 ($N = 42,256$; mean age 67 years; 71% women) and controls matched for age, sex and municipality of residence ($N = 83,618$).

Methods: information on purchases of prescription BZDRD, including the number of defined daily doses (DDDs), between 2012 and 2017 was obtained from the Dispensations Reimbursable under the National Health Insurance Scheme register. Background information was obtained from national registers.

Results: more caregivers than controls used BZDRD, both among women (users per 100 person-years: 17.2 versus 15.2, $P < 0.001$) and men (14.6 versus 11.8, $P < 0.001$). These differences were largely explained by hypnotic BZDRD use. There were also more long-term BZDRD users per 100 person-years among caregivers than controls, both among women (5.0 versus 4.3, $P = 0.001$) and men (5.3 versus 3.8, $P < 0.001$). Use of hypnotic BZDRD in number of DDDs was higher in caregivers than in controls, particularly among men above 50 years. Caregivers used more anxiolytic BZDRD than controls from middle age to 75 years but less in the oldest age groups.

Conclusions: higher level of BZDRD use among caregivers indicates that caregivers have more sleep and mental health problems than non-caregivers. Adequate treatment of these problems and support for caregiving should be ensured for caregivers.

Keywords: informal caregiving, ageing, mental disorders, psychoactive drugs, insomnia, older people

Key Points

- Caregivers used more benzodiazepines and related drugs (BZDRD) than controls.
- Higher level of BZDRD use may indicate more sleep and mental health problems in caregivers.
- Use of hypnotic BZDRD was high particularly among older caregivers.
- High levels of BZDRD use in caregivers are alarming as BZDRD may impair caregivers' health and capability to care.

Introduction

Benzodiazepines and related drugs (BZDRD) are commonly used drugs for e.g. insomnia and anxiety. BZDRD can have several adverse effects, such as falls [1] and cognitive decline [2], particularly among older people. Because the risks of BZDRD are likely to exceed their benefits in older people BZDRD are generally not recommended for this age group [3, 4]. However, use of BZDRD is high in this group [5–7].

Many adults who take care of another person because of functional limitations or long-term illness as family caregivers report mental health and sleep problems [8–12]. Nevertheless, use of BZDRD has not been studied in family caregivers previously. BZDRD use may serve as an objective indicator of sleep and mental health problems. On the other hand, due to the questionable benefit to risk ratio of BZDRD, BZDRD use could compromise family caregivers' capability to take care of another person, particularly among older caregivers. Therefore, BZDRD use needs to be studied among caregivers. The aim of this study was to examine whether the use of prescription BZDRD differs between family caregivers and matched controls in Finland using register-based data.

Methods

Material

This study included all individuals, who received family caregiver's allowance in Finland in the year 2012 ($N = 42,256$; mean age 67 (SD 16) years; median 70 years, 71% women) identified in the Finnish Tax Administration's register. Two controls—matched for birth year, sex and municipality of residence—per one caregiver were drawn from the register of the Population Register Centre ($N = 83,618$). The material has been described in detail elsewhere [13]. Data linkages were performed using personal identification codes.

Information on all reimbursed BZDRD (anatomical therapeutic chemical [ATC] codes: N03AE, N05BA, N05CD, N05CF and N06CA) purchases, including date of purchase, number of defined daily doses (DDD) purchased and ATC code, were obtained from the Dispensations Reimbursable under the National Health Insurance Scheme register of the Finnish Social Insurance Institution (SII) for the years 2012–17. DDD is the assumed average daily maintenance dose for a drug used for its main indication in adults. The register

contains pharmacy claims on all prescription drug purchases reimbursed to Finnish residents in non-institutional settings by the SII. BZDRD are not sold over the counter in Finland, and it is possible to purchase reimbursable prescription drugs only for a maximum of 3 months use at a time. BZDRD were categorised into anxiolytic (ATC codes N03AE, N05BA and N06CA) and hypnotic (N05CD and N05CF) BZDRD.

First, we determined the numbers of calendar years during which a subject had purchased anxiolytic BZDRD, hypnotic BZDRD and any BZDRD at least once and the numbers of years during which a subject was a long-term user i.e. had purchased BZDRD at least twice and 180 DDDs or more during a calendar year. Second, the total number of DDDs purchased during the 6-year follow-up and the number of DDDs per person-year in the follow-up was calculated for each individual and drug group. Information on education, income, emigrations and deaths were obtained from national registers as described earlier [13].

Statistical analysis

Follow-up time in person-years was calculated as the difference between 1 January 2012 and either the date of moving abroad, the date of death or 31 December 2017, whichever occurred first. The differences in the numbers of BZDRD (long-term) users between the caregivers and controls were analysed using Poisson regression models with the numbers of calendar years of BZDRD (long-term) use as the dependent variables and taking into account the follow-up time to yield prevalences per 100 person-years. Mean number of DDDs used per person-year during the follow-up was analysed using general linear models with Poisson distribution and log link function. Goodness-of-fit of these models were assessed using deviance and Pearson chi-squared tests, which showed a good fit in all models. Bonferroni correction for P -values was used to account for multiple tests. Negative binomial regression was used to analyse benzodiazepine use in number of DDDs as a function of age at baseline. Models included quadratic terms for age. The analyses were adjusted for education and income. Stata 17.0 (StataCorp LP; College Station, TX, USA) statistical package was used for the analysis.

Results

Background characteristics of the caregivers and controls are presented in [Appendix 1](#), (supplementary data are available in *Age and Ageing* online).

Table 1. BZDRD use in female and male caregivers and their controls in years 2012–17

	Women		p	Men		P
	Controls N = 59,141	Caregivers N = 29,846		Controls N = 24,477	Caregivers N = 12,410	
Anxiolytic BZDRD						
Users per 100 person-years (95% CI)	6.6 (6.4–6.8)	7.4 (7.1–7.6)	<0.001	5.0 (4.7–5.2)	5.9 (5.5–6.2)	0.002
Long-term users, per 100 person-years (95% CI)	1.9 (1.8–2.0)	2.1 (1.9–2.3)	0.63	1.6 (1.4–1.7)	2.1 (1.8–2.3)	0.003
DDD per person-year, mean (SEM)	8.98 (0.25)	9.58 (0.38)	0.98	8.30 (0.42)	9.86 (0.64)	0.35
Hypnotic BZDRD						
Users per 100 person-years (95% CI)	10.3 (10.1–10.5)	11.9 (11.6–12.3)	<0.001	8.0 (7.7–8.3)	10.4 (10.0–10.8)	<0.001
Long-term users, per 100 person-years (95% CI)	3.3 (3.1–3.4)	3.9 (3.6–4.1)	<0.001	2.7 (2.5–2.9)	4.0 (3.7–4.3)	<0.001
DDD per person-year, mean (SEM)	16.17 (0.31)	18.12 (0.39)	0.002	14.25 (0.39)	20.09 (0.68)	<0.001
All BZDRD						
Users per 100 person-years (95%)	15.2 (15.0–15.5)	17.2 (16.8–17.6)	<0.001	11.8 (11.4–12.2)	14.6 (14.0–15.2)	<0.001
Long-term users per 100 person-years	4.3 (4.2–4.5)	5.0 (4.8–5.3)	0.001	3.8 (3.5–4.0)	5.3 (4.9–5.6)	<0.001
DDD per person-year, mean (SEM)	25.15 (0.43)	27.70 (0.59)	0.005	22.56 (0.61)	29.95 (1.03)	<0.001

Notes. User is an individual who has purchased BZDRD at least once during a calendar year. CI, confidence interval; DDD, defined daily dose (typical daily dose for the main indication). Long-term user has had at least two purchases and ≥ 180 DDDs purchased during a calendar year. *P*-values corrected for multiple comparison using Bonferroni correction and adjusted for income and education.

A larger number of caregivers than controls were BZDRD users and long-term users among both women and men (Table 1). The only exception was the prevalence of long-term users of anxiolytic BZDRD in women that did not differ between caregivers and controls. Mean numbers of DDDs used were higher for all BZDRD and hypnotic BZDRD in both female and male caregivers than in controls but there were no differences between caregivers and controls in the numbers of DDDs used for anxiolytic BZDRD.

The number of DDDs of both anxiolytic and hypnotic BZDRD per person-year varied according to age at baseline (Figure 1). Anxiolytic BZDRD use peaked around age 50–70 years in both men and women and was higher in caregivers compared with controls, particularly among men. However, after the age of 80 years, anxiolytic BZDRD use was lower in both female and male caregivers compared with controls. Hypnotic BZDRD use, in turn, increased as a function of age in female caregivers and their controls, and was higher in female caregivers than controls after 45 years of age. In men, hypnotic BZDRD use increased as a function of age, but in male caregivers hypnotic BZDRD use accelerated ~ 40 years of age and stayed at a higher level compared with controls thereafter.

Discussion

Hypnotic BZDRD were used almost twice as much as anxiolytic BZDRD and use of hypnotic BZDRD largely explained the differences between caregivers and controls in BZDRD use. These findings indicate higher levels of sleep problems in caregivers than in non-caregivers. The findings support previous findings of surveys with self-reported outcomes, which have reported more sleep problems in caregivers than in non-caregivers [8, 9]. Several studies have also found more self-reported mental health

problems in caregivers compared with non-caregivers [9, 10] and caregivers appear to use more antidepressants than non-caregivers [14]. Insomnia and other mental health problems are often intertwined [15] and may follow from chronic stress [16, 17], which has been reported in previous caregiver studies especially in high-intensity caregivers [9, 18]. Caregivers included in the present study, i.e. those who receive caregiver's allowance in Finland, are high-intensity caregivers [13].

In line with previous studies on BZDRD use [5, 7], use of hypnotic BZDRD was highest among the oldest, who are at the highest risk for adverse effects of BZDRD. Although mean anxiolytic BZDRD use expressed as the number of DDDs did not differ between caregivers and controls when analysed over all age groups, there were differences when anxiolytic BZDRD use was analysed according to age. In female caregivers between 45 and 75 years and in male caregivers younger than 75 years, anxiolytic BZDRD use was higher compared with controls. Higher anxiolytic BZDRD use in controls in the oldest age groups is likely to reflect the effect of approaching death. Mortality is higher in the controls in this study sample, as reported earlier [13], i.e. they are closer to death than caregivers, and BZDRD use has been found to increase with approaching death [19]. Consequently, BZDRD use may be underestimated in all caregivers but more so in the oldest age groups.

Strengths of this study include the large, nation-wide sample and representative and robust data on prescription purchases, with no loss to follow up [20]. Based on the statistics of BZDRD wholesale as number of DDDs, 93–97% of the BZDRD were sold to pharmacies for outpatient care in Finland in 2012–17 [21, 22]. These figures also include non-reimbursed medicines and hence, the coverage of the register used in the present study is likely to be somewhat lower especially as temazepam, a commonly used hypnotic BZDRD, has been non-reimbursable since

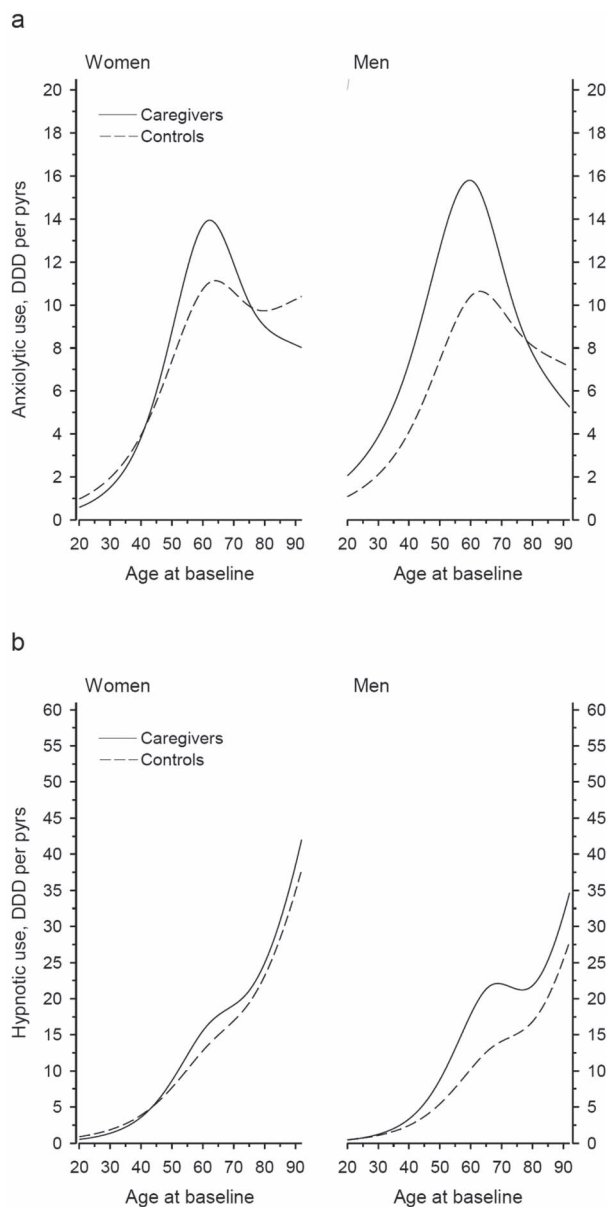


Figure 1. Anxiolytic (a) and hypnotic (b) BZDRD use in number of defined daily doses (DDDs) per person-year (pyrs) for family caregivers (continuous line) and controls (dashed line) as a function of age at baseline.

2013 [7]. A limitation is also the lack of data on the clinical indications for BZDRD prescriptions. In older subjects, use of DDD as an estimate of the daily dose may underestimate the actual number of doses of BZDRD used because lower dosages of BZDRD are recommended for them.

High levels of BZDRD use in caregivers, particularly in older caregivers, require attention. Use of BZDRD might compromise caregiver's health and capability to care. Hence, caregivers should have access to effective and safe therapies for their sleep and mental health problems. However, such therapies may have a limited effect if the root cause of the problems is the very demanding caregiving situation as

therapies do not remove the root cause [23]. In those cases, lightening of the caregiver's burden could be the answer.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Aging* online.

Availability of Data and Materials: The data that support the findings of this study are available from Finnish Tax Administration, and Finnish Social and Health Data Permit Authority (Findata) but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Finnish Tax Administration, and Findata.

Declaration of Conflicts of Interest: Tuija M. Mikkola has received family caregiver's allowance from the City of Vantaa. The rest of the authors report no conflicts of interest.

Declaration of Sources of Funding: This work was supported by Samfundet Folkhälsan, Medicinska Understödsföreningen, Liv och Hälsa r.f., and Signe and Ane Gyllenberg Foundation. The funding bodies had no role in study design or collection, analysis and interpretation of data or in writing the manuscript or in decision to submit the work for publication.

Ethical Declaration: The study plan was approved by the Ethics Committee of the Helsinki and Uusimaa Health Care District (HUS/1955/2018).

References

1. Seppala LJ, Wermelink AMAT, de Vries M *et al.* Fall-risk-increasing drugs: a systematic review and meta-analysis: II. Psychotropics. *J Am Med Dir Assoc* 2018; 19: 371.e11–7.
2. Crowe SF, Stranks EK. The residual medium and long-term cognitive effects of benzodiazepine use: an updated meta-analysis. *Arch Clin Neuropsychol* 2018; 33: 901–11.
3. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *Br Med J* 2005; 331: 1169–73.
4. Schroeck JL, Ford J, Conway EL *et al.* Review of safety and efficacy of sleep medicines in older adults. *Clin Ther* 2016; 38: 2340–72. <https://doi.org/10.1016/j.clinthera.2016.09.010>.
5. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiat* 2015; 72: 136–42.
6. Neutel CI, Skurtveit S, Berg C. What is the point of guidelines? Benzodiazepine and z-hypnotic use by an elderly population. *Sleep Med* 2012; 13: 893–7.
7. Kurko T, Saastamoinen LK, Tuulio-Henriksson A *et al.* Trends in the long-term use of benzodiazepine anxiolytics and hypnotics: a national register study for 2006 to 2014. *Pharmacoepidemiol Drug Saf* 2018; 27: 674–82.
8. DePasquale N, Sliwinski MJ, Zarit SH, Buxton OM, Almeida DM. Unpaid caregiving roles and sleep among women working in nursing homes: a longitudinal study. *Gerontologist* 2019; 59: 474–85.
9. Koyanagi A, DeVlyder JE, Stubbs B *et al.* Depression, sleep problems, and perceived stress among informal caregivers in

- 58 low-, middle-, and high-income countries: a cross-sectional analysis of community-based surveys. *J Psychiatr Res* 2018; 96: 115–23.
10. Smith L, Onwumere J, Craig T, McManus S, Bebbington P, Kuipers E. Mental and physical illness in caregivers: results from an English national survey sample. *B J Psych* 2014; 205: 197–203.
 11. Hiel L, Beenackers MA, Renders CM, Robroek SJW, Burdorf A, Croezen S. Providing personal informal care to older European adults: should we care about the caregivers' health? *Prev Med (Baltim)* 2015; 70: 64–8.
 12. Kaschowitz J, Brandt M. Health effects of informal caregiving across Europe: a longitudinal approach. *Soc Sci Med* 2017; 173: 72–80.
 13. Mikkola TM, Kautiainen H, Mänty M, von Bonsdorff MB, Kröger T, Eriksson JG. Age-dependency in mortality of family caregivers: a nationwide register-based study. *Aging Clin Exp Res* 2021; 33: 1971–80.
 14. Mikkola TM, Kautiainen H, Mänty M *et al.* Use of antidepressants among Finnish family caregivers: a nationwide register based study. *Soc Psychiatry Psychiatr Epidemiol* 2021; 56: 2209–16.
 15. Palagini L, Hertenstein E, Riemann D, Nissen C. Sleep, insomnia and mental health. *J Sleep Res* 2022; 31: e13628. <https://doi.org/10.1111/jsr.13628>.
 16. Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. *Gerontologist* 1990; 30: 583–94.
 17. Song Y, Harrison SL, Martin JL *et al.* Changes in caregiving status and intensity and sleep characteristics among high and low stressed older women. *J Clin Sleep Med* 2017; 13: 1403–10.
 18. Lyons JG, Cauley JA, Fredman L. The effect of transitions in caregiving status and intensity on perceived stress among 992 female caregivers and noncaregivers. *J Gerontol A Biol Sci Med Sci* 2015; 70: 1018–23.
 19. Neutel CI, Johansen HL. Association between hypnotics use and increased mortality: causation or confounding? *Eur J Clin Pharmacol* 2015; 71: 637–42.
 20. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol* 2009; 106: 86–94.
 21. Finnish Statistics on Medicines 2017. Helsinki: Finnish Medicines Agency Fimea and Social Insurance Institution, 2018.
 22. Finnish Statistics on Medicines 2014. Helsinki: Finnish Medicines Agency Fimea and Social Insurance Institution, 2015.
 23. Hiel L, Beenackers MA, Renders CM, Robroek SJW, Burdorf A, Croezen S. The structure of risk factors and outcomes for family caregivers: implications for assessment and treatment. *Aging Ment Health* 2010; 14: 220–31.

Received 25 April 2022; editorial decision 1 September 2022