Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study

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ABSTRACT

OBJECTIVE
To determine whether higher cumulative use of benzodiazepines is associated with a higher risk of dementia or more rapid cognitive decline.

DESIGN
Prospective population based cohort.

SETTING
Integrated healthcare delivery system, Seattle, Washington.

PARTICIPANTS
3434 participants aged ≥65 without dementia at study entry. There were two rounds of recruitment (1994-96 and 2000-03) followed by continuous enrollment beginning in 2004.

MAIN OUTCOMES MEASURES
The cognitive abilities screening instrument (CASI) was administered every two years to screen for dementia and was used to examine cognitive trajectory. Incident dementia and Alzheimer’s disease were determined with standard diagnostic criteria. Benzodiazepine exposure was defined from computerized pharmacy data and consisted of the total standardized daily doses (TSDDs) dispensed over a 10 year period (a rolling window that moved forward in time during follow-up). The most recent year was excluded because of possible use for prodromal symptoms. Multivariable Cox proportional hazard models were used to examine time varying use of benzodiazepine and dementia risk. Analyses of cognitive trajectory used linear regression models with generalized estimating equations.

RESULTS
Over a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia, of whom 637 developed Alzheimer’s disease. For dementia, the adjusted hazard ratios associated with cumulative benzodiazepine use compared with non-use were 1.25 (95% confidence interval 1.03 to 1.51) for 1-30 TSDDs; 1.31 (1.00 to 1.71) for 31-120 TSDDs; and 1.07 (0.82 to 1.39) for ≥121 TSDDs. Results were similar for Alzheimer’s disease. Higher benzodiazepine use was not associated with more rapid cognitive decline.

CONCLUSION
The risk of dementia is slightly higher in people with minimal exposure to benzodiazepines but not with the highest level of exposure. These results do not support a causal association between benzodiazepine use and dementia.

Introduction
Benzodiazepines are widely prescribed to treat insomnia and anxiety, with about 9-12% of older adults in the United States reporting use.1,2 These drugs are associated with many deleterious effects, including falls, fractures, traffic incidents, and delirium.3-5 Because of these risks benzodiazepines are not recommended for treatment of insomnia, agitation, or delirium in older adults, and it is recommended that use, if any, be short term.6 Nonethe- less, benzodiazepine use increases with age, and older adults are more likely to use these drugs long term.7

Single dose studies have shown that benzodiazepines impair aspects of cognition (such as memory and attention).8-10 It remains uncertain whether long term use is associated with global cognitive decline. Some well conducted studies suggest that long term use does not increase the risk of cognitive decline, but results are conflicting.6,7 Considerable attention has focused on the potential relation between benzodiazepines and increased risk of dementia.7,8,11 Examination of this relation is challenging because dementia can be preceded by symptoms such as insomnia, anxiety, and depression,12,13 which are often treated with benzodiazepines. Observational studies must use appropriate design strategies to account for benzodiazepines used to treat early symptoms of dementia to avoid bias from reverse causation. We are aware of three studies that intentionally considered the prodromal phase and potential for reverse causation. Two of these reported an increased risk of dementia with benzodiazepine use,6,8 while the other did not.14 These studies had limitations including lack of information about duration and dose of benzodiazepine treatment6 and the reliance on administrative data to identify people with Alzheimer’s disease.9,14 No studies have been conducted in the US, where patterns of benzodiazepine use differ from other countries. Given the enormous public health implications, we need a better understanding of the potential cognitive risks of cumulative benzodiazepine use.

We used data from a prospective cohort study with research quality diagnoses of dementia and computerized pharmacy data to evaluate the association...
between cumulative benzodiazepine use and the risk for dementia and cognitive decline. We hypothesized that higher cumulative use would be associated with increased risk.

**Methods**

**Design, study setting, and participants**

The Adult Changes in Thought study is a population based prospective cohort study conducted within Group Health, an integrated healthcare delivery system in the north west US. Study procedures have been reported elsewhere. Briefly, participants aged ≥65 without dementia were randomly sampled from Group Health members in the Seattle area. The original cohort of 2581 people was enrolled in 1994-96 and 811 additional participants in 2000-03. In 2004 the study began continuous enrollment to replace those who developed dementia, died, or dropped out. Participants were assessed at study entry and biennially thereafter to evaluate cognitive function and collect demographic characteristics, medical history, health behaviors, and health status. Our analyses were limited to participants who had at least 10 years of prior membership of Group Health at enrollment to ensure adequate data on long term exposure to medication (fig 1). For the analyses of dementia, we required participants to have at least one follow-up visit. For the analyses of cognitive trajectory, we included all participants who had a valid cognitive score at baseline. Because we were interested in whether benzodiazepine use was associated with a more rapid cognitive decline only in participants who had not yet had a diagnosis of dementia, we excluded from these analyses any visits made after the date of onset of dementia.

**Cognitive outcomes**

*Identification of dementia and Alzheimer’s disease*

We used the cognitive abilities screening instrument (CASI) to screen for dementia at study entry and at each biennial study visit. Scores range from 0 to 100, with higher scores indicating better performance. Participants with scores of ≤85 underwent a standardized diagnostic evaluation for dementia, including a physical and neurological examination and neuropsychological testing. The results, along with clinical data from participants’ medical records, were then reviewed in a multidisciplinary consensus conference including the examining physician, a neuropsychologist, another study physician, and the study nurse. The diagnoses of dementia and Alzheimer’s disease were made with standard research criteria. The date of onset of dementia was assigned as the midpoint between the study visit that triggered the evaluation of dementia and the preceding visit. Participants with new onset dementia underwent at least one follow-up examination to confirm the diagnosis.

**Use of benzodiazepines**

The exposure included benzodiazepines and non-benzodiazepine hypnotics that bind to the gamma-aminobutyric acid (GABA) receptor, such as zolpidem, zaleplon, and eszopiclone. Few participants, however, used non-benzodiazepine hypnotics. Drug use was ascertained from Group Health’s computerized pharmacy data and included drug name, strength, route of administration, date dispensed, and amount dispensed.

Previous studies have not delineated what pattern of benzodiazepine exposure might be important for increasing risk of dementia (for example, long term sustained use versus several episodes of periodic use). We hypothesized that cumulative drug exposure, particularly heavier exposure that might accumulate over a long time period (via either intermittent or sustained use), was the most plausible causal mechanism by which use might increase the risk of dementia. We therefore selected a 10 year window based on this hypothesis and on methodologic and practical considerations.

To create our exposure measures, we first calculated the total benzodiazepine dose for each prescription by multiplying the drug strength and the number of tablets dispensed. We then calculated a standardized daily dose (SDD) by dividing the product by the minimum effective dose per day recommended for use in older adults (table 1). For each participant, we summed the SDDs for all filled prescriptions for benzodiazepines during the 10 year exposure window to create a cumulative total standardized daily dose (TSDD). We constructed a time varying measure defined as the TSDD dispensed over a
10 year window after excluding dispensings in the most recent year, which could have been for prodromal symptoms of dementia. Figure 2 shows how exposure windows were defined. At each time point during follow-up, the cumulative exposure for all participants at risk is recalculated by summing all of their benzodiazepine use in the previous 10 years (after exclusion of the most recent year). We categorized cumulative use as no use, 1-30 TSDDs, 31-120 TSDDs, or ≥121 TSDDs based on the distribution of the exposure and clinically meaningful cutpoints. As examples, a person would reach the highest level of exposure in a 10 year period if he/she took any of the following for a total of 121 days or longer: temazepam 15 mg/day, triazolam 0.125 mg/day, or lorazepam 2 mg/day. This level of use could be achieved by daily use for 121 days or could represent episodic use over several years.

Our exposure for the analyses of cognitive trajectory differed in a few ways from the one we defined for analyses of dementia. First, cumulative benzodiazepine use was calculated in the 10 years immediately before each study visit (that is, no one year lag) as we were evaluating cognitive decline only in participants who had not yet had a diagnosis of dementia. Second, we created a measure of recent use defined as filling two or more prescriptions for a benzodiazepine in the six months before each visit, requiring each prescription to have at least seven TSDDs (fig 2).

### Covariates

Information about covariates came from standardized questionnaires administered at each study visit and from Group Health's electronic databases. Demographic factors included age, sex, and years of education. Body mass index (BMI) was determined from measured height and weight. Participants were asked about smoking, exercise, and self rated health. We ascertained presence of several comorbidities including hypertension or diabetes mellitus treated with drugs (computerized pharmacy data), history of stroke (self report or electronic databases), and coronary heart disease (self report). Symptoms of depression were obtained from the short version of the Center for Epidemiologic Studies Depression scale.

### Statistical analyses

**Analyses of dementia and Alzheimer's disease**

We used separate multivariable Cox proportional hazards models with participant’s age as the time scale to estimate hazard ratios and 95% confidence intervals for the association between benzodiazepine use and incident dementia or possible or probable Alzheimer’s disease. Age at study entry was taken as start of follow-up. Participants were followed until the earliest of onset of dementia, disenrollment from Group Health, or last study visit before 30 September 2012. We adjusted for age at study entry, sex, educational level, hypertension, diabetes mellitus, current smoking, stroke, coronary heart disease, BMI, regular exercise, self rated health, and symptoms of depression (variables defined in table 2).

We included time varying measures for coronary heart disease analyses.
disease and stroke and the values from the baseline visit for all other covariates. We excluded observations with missing covariate information (n=130). We assessed the assumption of proportional hazards by testing the interaction between the exposure and age at follow-up. In secondary analyses, we modeled the exposure as a continuous variable using natural cubic splines to examine whether results were influenced by the cutpoints chosen for exposure categories.

Analyses of cognitive trajectory
We evaluated the average differences in CASI scores and the average differences in rates of decline of these scores between benzodiazepine user groups using linear regression models estimated via generalized estimating equations. We used a working independence correlation matrix and calculated standard errors using the Huber-White sandwich estimator to account for the correlation between multiple CASI scores from the same individual.22 We estimated the average difference in rate of cognitive decline, defined as decline in CASI per year, between user groups by including an interaction term between age at follow-up and level of cumulative exposure. Models adjusted for the same covariates as in the dementia analyses. Analyses of the association between CASI trajectory and recent benzodiazepine use (six months before visit) also adjusted for cumulative use (six months to 10 years before visit).

Sensitivity analyses
For the dementia analyses, we performed several sensitivity analyses to explore the robustness of our results. Given the uncertainty regarding whether prodromal symptoms might first emerge before a diagnosis of dementia, we extended the lag time to two years. In additional models, we included depressive symptoms as a time varying covariate and adjusted for the Charlson comorbidity index (Deyo adaption).20 Lastly, we performed a post hoc analysis extending the lag time to five years to replicate the methods used by another study.2

All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

Patient involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in recruitment or the design and implementation of the study. There are no plans to involve patients in the dissemination of results.

Results
Table 2 shows participants’ characteristics overall and by cumulative benzodiazepine exposure in the 10 years before study entry. The median age of participants at study entry was 74, 91% (n=3314) were white, 60% were women, and most (66%) had some college education. Overall, 30% had filled at least one prescription for a benzodiazepine in the 10 years before study entry, though only 3% (n=98) had recently used a benzodiazepine (within six months). Participants with heavier benzodiazepine use were more likely to be women and report fair or poor self rated health, have more depressive symptoms, and have comorbidities (such as hypertension, stroke, and coronary heart disease) than non-users. The most common benzodiazepines were temazepam, diazepam, clonazepam, triazolam, and lorazepam (table 3), which together accounted for 83% of the benzodiazepine exposure. Within the highest benzodiazepine category (≥121 TSDDs), the median level of use was 375 TSDDs (equivalent to slightly over a year of daily use).

Dementia and Alzheimer’s disease
The 3434 participants included in these analyses accrued 25 019 person years of follow-up, with a mean of 7.3 (SD 4.8) years. During this time, 797 (23.2%)...
Table 3 | Any and cumulative benzodiazepine use during study period*

| Drug          | No (%) of all participants (n=3436) | Total TSDD filled (% of total) |
|---------------|-----------------------------------|-------------------------------|
| Temazepam     | 540 (15.7)                        | 117349 (21.8)                |
| Diazepam      | 508 (14.8)                        | 90085 (16.7)                 |
| Clonazepam    | 77 (2.2)                          | 88038 (16.3)                 |
| Triazolam     | 265 (7.7)                         | 76899 (14.3)                 |
| Lorazepam     | 612 (17.8)                        | 72405 (13.4)                 |
| Alprazolam    | 227 (6.6)                         | 27765 (5.2)                  |
| Zolpidem      | 126 (3.7)                         | 25929 (4.8)                  |
| Flurazepam    | 97 (2.8)                          | 23994 (4.5)                  |
| Oxazepam      | 85 (2.5)                          | 12298 (2.3)                  |
| Chlordiazepoxide | 47 (1.4)                     | 3097 (0.6)                   |
| Clorazepate   | 5 (0.2)                           | 1193 (0.2)                   |
| Eszopiclone   | 3 (0.1)                           | 159 (0.0)                    |
| Zaleplon      | 2 (0.1)                           | 62 (0.0)                     |
| Total         | —                                 | 539272                       |

TSDD=total standardized daily dose.

*Participant’s study period included 10 years before study entry up to time of diagnosis of dementia or censored.

Table 4 | Follow-up time and number of events according to exposure category

| TSDD | Follow-up time (person years) | Dementia cases | Alzheimer’s disease cases |
|------|-------------------------------|---------------|--------------------------|
| 0    | 16849                         | 511           | 418                      |
| 1-30 | 4099                          | 148           | 120                      |
| 31-120 | 1590                        | 63            | 43                       |
| ≥121 | 2481                          | 75            | 56                       |

TSDD=total standardized daily dose.

Discussion

In this population-based longitudinal study of older adults with detailed pharmacy data and rigorous outcome assessment, we did not find any association between the highest level of benzodiazepine use and dementia or cognitive decline. Contrary to expectations, we found a small increased risk for dementia in people with low (that is, up to one month) or moderate (one to four months) use. This pattern does not support a causal association between cumulative benzodiazepine use and risk of dementia, and the small increased risk observed with low use could represent treatment of prodromal symptoms, as supported by our sensitivity analyses. It is also possible that people with prodromal dementia, even years before diagnosis, could be more sensitive to benzodiazepine induced acute cognitive adverse events (for example, delirium), resulting in discontinuation of the drug and avoidance, in turn leading to low levels of use.

Comparison with other studies

Of the studies that used strategies to deal with reverse causation, our findings are in line with one recent study but are in contrast with two previous studies that reported an increased risk of dementia with benzodiazepine use. In a case-control study conducted using administrative data from the UK based Clinical Practice Research Datalink, high use of benzodiazepines, as determined by number of prescriptions, was not associated with an increased risk of Alzheimer’s disease after use initiated in the prodromal phase was between 1.1 and 1.4 for ≤90 TSDDs but risk declined toward 1.0 with higher exposure. Benzodiazepine use was not significantly associated with Alzheimer’s disease at any exposure level.

When we extended the lag time to two years, the associations for the lowest level of benzodiazepine use were no longer significant for either dementia (hazard ratio 1.18, 95% confidence interval 0.97 to 1.44) or Alzheimer’s disease (1.18, 0.95 to 1.47) (fig 3). Adjustment for depressive symptoms as a time varying covariate or for overall comorbidity did not alter estimates appreciably. In the post hoc analysis with a five year lag, we continued to find no association between cumulative benzodiazepine use and dementia (table 5).
Alzheimer's disease
1-30 TSDD
Age adjusted
Multivariable adjusted 1 year lag
Multivariable adjusted 2 year lag
31-120 TSDD
Age adjusted
Multivariable adjusted 1 year lag
Multivariable adjusted 2 year lag
≥121 TSDD
Age adjusted
Multivariable adjusted 1 year lag
Multivariable adjusted 2 year lag

Multivariable adjusted (2008) year lag
Multivariable adjusted (2006) year lag
Multivariable adjusted (2005) year lag

≥0 TSDD
Age adjusted
Multivariable adjusted 1 year lag
Multivariable adjusted 2 year lag

≥0 TSDD
Age adjusted
Multivariable adjusted 1 year lag
Multivariable adjusted 2 year lag

Dementia
1-30 TSDD
Age adjusted
Multivariable adjusted 1 year lag
Multivariable adjusted 2 year lag
31-120 TSDD
Age adjusted
Multivariable adjusted 1 year lag
Multivariable adjusted 2 year lag
≥121 TSDD
Age adjusted
Multivariable adjusted 1 year lag
Multivariable adjusted 2 year lag

Fig 3 | Hazard ratios for all cause dementia and Alzheimer’s disease for each level of cumulative benzodiazepine exposure compared with no use. Multivariable models adjusted for study cohort, age at study entry, sex, educational level, hypertension, diabetes mellitus, current smoking, stroke, coronary heart disease, BMI, regular exercise, self-rated health, and depressive symptoms

Fig 4 | Association between cumulative benzodiazepine use modeled as spline and risk of incident dementia or Alzheimer’s disease

Table 5 | Association between incident dementia and Alzheimer’s disease and six year cumulative benzodiazepine use with five year lag time.*† Figures are hazard ratios (95% CI)

| TSDD# | Adjusted model$ |
|-------|-----------------|
| 0     | 1.00 (Reference) |
| 1-30  | 1.21 (0.98 to 1.50) |
| 31-120| 1.20 (0.88 to 1.64) |
| ≥121  | 1.13 (0.85 to 1.52) |

Alzheimer’s disease
| TSDD# | Adjusted model$ |
|-------|-----------------|
| 0     | 1.00 (Reference) |
| 1-30  | 1.24 (0.98 to 1.57) |
| 31-120| 1.04 (0.72 to 1.51) |
| ≥121  | 1.05 (0.75 to 1.46) |

TSDD = total standardized daily dose; ACT = Adult Changes in Thought.
*Observations with missing adjustment variables excluded from model (n=130, 3.6%).
†Prescriptions in five years before dementia onset excluded from calculation of exposure.
‡TSDD example—minimum effective daily dose for temazepam is 15 mg daily (=1 TSDD); person would fall into following TSDD category if they were using 15 mg daily for 15 days (TSDD 1-30); 15 mg daily for 90 days (TSDD 31-120); 15 mg daily for 6 months (TSDD ≥121).
§Adjusted for ACT cohort, age (via the time-axis), age at ACT study entry, sex, educational level, BMI, current smoking, regular exercise, self-rated health, hypertension, diabetes mellitus, stroke, coronary heart disease, history of high depressive symptoms.

accounted for. In fact, people who filled more than 100 benzodiazepine prescriptions had a lower risk for Alzheimer’s disease than non-users, a finding the authors cautioned against overinterpreting.14 In contrast, in a prospective population based study conducted in France of 1063 older adults, new use of benzodiazepines was associated with an increased risk of dementia (hazard ratio 1.62, 95% confidence interval 1.08 to 2.43).8 In regard to this latter study, our results are not directly comparable because of differences in study design (their study included new users) and method of ascertaining benzodiazepine use (they relied on periodic interviews and lacked information about dose, duration, or chronicity of use). The study lacked information on some potential confounders and excluded 72% of the sample because of the new user design. In a case-control study among older adults living in Quebec, benzodiazepine use as assessed by computerized pharmacy data five to 10 years before the index date was associated with increased risk of Alzheimer’s disease.8 These authors reported a dose-response relation with no association found for a cumulative dose of less than or equal to 91 prescribed daily doses but an increased risk for 91-180 prescribed daily doses (1.32, 1.01 to 1.74) and >180 prescribed daily doses (1.84, 1.62 to 2.08). After adjustment for diagnoses of depression, anxiety, and insomnia, estimated effects were slightly attenuated, and only the highest use category remained significantly associated with risk of Alzheimer’s disease.

It is unclear why our findings differ from those of the Canadian study, but we offer a few possible explanations. Our participants could have had considerably lower use of benzodiazepines, although this is difficult to determine as that study did not report additional details about extent of exposure in their highest use category. If there is a true association, perhaps cumulative

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use in our study fell below the threshold needed to increase risk of dementia. Although the method to calculate and categorize the cumulative daily dose differed in these studies, it is unlikely that these differences explain our discrepant results. Our analysis using continuous benzodiazepine exposure supported our primary findings of no association with higher doses. We explored extending the lag period used to exclude prescriptions because of prodromal symptoms to more closely match the Canadian study and continued to find no association. The primary difference between this study and ours relates to ascertainment of the outcome. The Canadian study relied on administrative data to identify cases of Alzheimer’s disease; therefore, detection of Alzheimer’s disease could be delayed compared with routine surveillance as used in our study, and there could be considerable misclassification of outcome status, which could be differential. People with heavy benzodiazepine use might have more frequent contact with the healthcare system, which could result in a higher likelihood of dementia being recognized and coded. While we cannot entirely rule out a moderate increase in a higher likelihood of dementia being recognized and coded, it is challenging to identify true “new users,” particularly in elderly people. A prior study that attempted to identify new users in fact had limited data about benzodiazepine use before study enrollment, and so their apparent “new users” could in fact have had a history of benzodiazepine use, suggesting that even this study could have experienced bias because of depletion of susceptibles.

**Strengths and limitations**

Our study has several strengths, including a large community based sample, an average follow-up of more than seven years, rigorous prospective ascertainment of dementia and Alzheimer’s disease, and the ability to examine subclinical cognitive decline and dementia in the same cohort. We used computerized pharmacy data to characterize benzodiazepine use 10 years before

| Table 6 | Difference in mean cognitive scores by levels of cumulative benzodiazepine use with no use as reference category |
|---------|-----------------------------------------------------------------------------------------------------------------|
| TSDD   | CASI Age adjusted (95% CI) | Multivariable adjusted (95% CI) | CASI-IRT† Age adjusted (95% CI) | Multivariable adjusted (95% CI) |
| 1-30   | −0.16 (−0.46 to 0.14) | −0.11 (−0.39 to 0.16) | −0.01 (−0.06 to 0.03) | −0.02 (−0.06 to 0.02) |
| 31-120 | −0.08 (−0.49 to 0.34) | 0.16 (−0.22 to 0.54) | 0.01 (−0.06 to 0.07) | 0.03 (−0.03 to 0.09) |
| ≥121  | −0.37 (−0.78 to 0.04) | −0.17 (−0.57 to 0.23) | −0.05 (−0.12 to 0.01) | −0.04 (−0.10 to 0.02) |

TSDD = total standardized daily dose; CASI = cognitive abilities screening instrument; IRT = item response theory; ACT = Adult Changes in Thought.

†Linear regression with generalized estimating equations to account for repeated observations per participant.

‡CASI-IRT had mean score of 0 (SD 1) among individuals without dementia at their most recent study visit.

§Model adjusted for ACT cohort, age at study entry, sex, education, hypertension, diabetes, current smoking, stroke, coronary heart disease, BMI, regular exercise, self rated health, and depressive symptoms.

| Table 7 | Difference in rate of change by levels of cumulative benzodiazepine use with no use as reference category |
|---------|---------------------------------------------------------------------------------------------------|
| TSDD   | CASI Age adjusted (95% CI) | Multivariable adjusted (95% CI) | CASI-IRT† Age adjusted (95% CI) | Multivariable adjusted (95% CI) |
| 1-30   | 0.001 (−0.04 to 0.05) | 0.006 (−0.04 to 0.05) | −0.0001 (−0.01 to 0.01) | 0.0002 (−0.01 to 0.01) |
| 31-120 | 0.032 (−0.03 to 0.09) | 0.043 (−0.01 to 0.10) | 0.0059 (0.00 to 0.01) | 0.0064 (0.00 to 0.01) |
| ≥121  | −0.002 (−0.06 to 0.06) | 0.002 (−0.05 to 0.06) | −0.0006 (−0.01 to 0.01) | 0.0007 (−0.01 to 0.01) |

TSDD = total standardized daily dose; CASI = cognitive abilities screening instrument; IRT = item response theory; ACT = Adult Changes in Thought.

†Positive values mean exposure category had slower decline with age than reference group.

‡CASI-IRT had mean score of 0 (SD 1) among individuals without dementia at their most recent study visit.

§Model adjusted for ACT cohort, age at study entry, sex, education, hypertension, diabetes, current smoking, stroke, coronary heart disease, BMI, regular exercise, self rated health, and depressive symptoms.
We defined our exposure groups using a 10 year exposure window, and our highest group is likely to include susceptible users of benzodiazepines might have developed dementia at a younger age and therefore been ineligible for study enrollment, which could have biased our findings toward not finding an association. We were unable to exclude the possibility that within the source population, the most susceptible users of benzodiazepines might have developed dementia at a younger age and therefore been ineligible for study enrollment, which could have biased our findings toward not finding an association.

We thank Susan McCurry, Wayne McCormick, and James Bowen, who participated in multidisciplinary consensus committee meetings that determined study participants’ dementia status. This paper was presented at the 30th Annual HMO Research Network Conference in Phoenix, AZ, on 3 April 2014.

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Clinical implications and conclusions

In conclusion, we found a slightly higher risk of dementia in people with the lowest benzodiazepine use but no increased risk in those with the highest level of exposure (median exposure equivalent to about one year of daily use). Overall, our pattern of findings does not support the theory that cumulative benzodiazepine use at the levels observed in our population is causally related to an increased risk for dementia or cognitive decline. It should be noted that our study did not examine the acute cognitive adverse events that can occur when treatment with a benzodiazepine is started in older adults and careful monitoring is recommended in this situation. Nonetheless, given the mixed evidence regarding benzodiazepines and risk of dementia and that these drugs are associated with many adverse events, healthcare providers are still advised to avoid benzodiazepines in older adults to prevent important adverse health outcomes, withdrawal, and dependence.

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Transparency declaration: SLG affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) are explained.

Data sharing: No additional data available.

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