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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 benzodiazepine use is associated with higher dementia risk or more rapid cognitive decline.

DESIGN: Prospective population-based cohort.

SETTING: Integrated health-care delivery system, Seattle, Washington

PARTICIPANTS: 3,434 participants aged 65 and older without dementia at study entry. There were two rounds of recruitment (1994-1996 and 2000-2003) followed by continuous enrollment beginning in 2004.

MAIN OUTCOMES MEASURES: The Cognitive Abilities Screening Instrument (CASI) was administered every 2 years to screen for dementia and was used to examine cognitive trajectory. Incident dementia and Alzheimer's disease were determined using 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). We excluded the most recent 1 year because of possible prodromal symptoms. Multivariable Cox proportional hazard models were used to examine time-varying benzodiazepine use and dementia risk. Analyses of cognitive trajectory used linear regression models estimated with generalized estimating equations.

RESULTS: Over a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia (637 developed Alzheimer's disease). For dementia, the adjusted hazard ratios (HRs) associated with cumulative benzodiazepine use compared to non-use were 1.25 (95% confidence interval [CI] 1.03 to 1.51) for 1 to 30 TSDDs; 1.31 (1.00 to 1.71) for 31 to120 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: We found slightly higher dementia risk in people with minimal benzodiazepine exposure, but not with the highest level of exposure. Overall our results do not support a causal association between benzodiazepine use and dementia. Health care providers are still advised to limit benzodiazepine use in older adults to avoid other significant adverse events.

Key words: dementia, Alzheimer's disease, pharmacoepidemiology, cohort study, benzodiazepine, aged

INTRODUCTION

Benzodiazepines are widely prescribed to treat insomnia and anxiety with approximately 9-12% of older adults in the United States reporting use.[1,2] These medications are associated with many deleterious effects, including falls, fractures, traffic accidents and delirium. [1,3] 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.[4] Nonetheless, benzodiazepine use increases with age, and older adults are more likely to use therapy long-term.[1]

Single dose studies document that benzodiazepines impair aspects of cognition (e.g. memory, attention).[5] 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 risk for cognitive decline, but results are conflicting.[6,7] Considerable attention has focused on the potential relationship between benzodiazepines and increased dementia risk.[8-14] Examining this relationship is challenging because dementia may be preceded by symptoms such as insomnia, anxiety, and depression,[15-17] symptoms that are often treated with benzodiazepines. Observational studies must employ appropriate design strategies to account for benzodiazepines used for treatment of early dementia symptoms to avoid bias due to reverse causation. We are aware of 3 studies that intentionally considered the prodromal phase and potential for reverse causation. Two of these reported increased dementia risk with benzodiazepine use,[8,9] while the other did not.[14] These studies had limitations including lack of information about benzodiazepine duration and dose,[8] and the reliance on administrative data to identify Alzheimer's disease cases.[9,14] No studies have been conducted in the United States, where patterns of benzodiazepine use differ from other countries. Given the enormous public health

implications, a better understanding of the potential cognitive risks of cumulative benzodiazepine use is needed.

We used data from a prospective cohort study with research-quality dementia diagnoses 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 health-care delivery system in the northwest US. Study procedures have been reported elsewhere.[18] Briefly, participants aged 65 years and older without dementia were randomly sampled from Seattle-area Group Health members. The original cohort of 2,581 people was enrolled between 1994 and 1996 and an additional 811 participants between 2000 and 2003. In 2004 the study began continuous enrollment to replace those who develop dementia, die or drop 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 Group Health membership at enrollment to ensure adequate data on long-term medication exposure (Figure 1). For the dementia analyses, we required participants to have at least one follow-up visit. For the cognitive trajectory analyses, 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 been diagnosed with dementia, we excluded from these analyses

visits after the date of dementia onset. The research protocol for this study was approved by the Group Health and University of Washington institutional review boards. Written informed consent was obtained from all participants.

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 each biennial study visit.[19] CASI scores range from 0 to 100 with higher scores indicating better performance. Participants with CASI scores of 85 or less underwent a standardized dementia diagnostic evaluation, 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 using standard research criteria.[20,21] The date of dementia onset was assigned as the midpoint between the study visit triggering the dementia evaluation and the preceding visit. Participants with new onset dementia underwent at least one follow-up examination to confirm the diagnosis.

Cognitive Trajectory

We used the CASI score for our primary analyses of cognitive trajectory. A feature of the CASI is that the distribution of item difficulty is not uniform across cognitive ability level. For example, there are few hard questions that would be appropriate for those with no cognitive impairment. Because of this, there is a nonlinear relationship between CASI score and underlying cognitive ability resulting in imprecision at the higher end of the scale.[22] Thus, we performed secondary analyses after applying item response theory (IRT) methods to generate

CASI-IRT scores which have linear scaling properties (Parscale, Scientific Software International Inc, Chicago, Illinois).[23] This addresses the relative insensitivity of the CASI to detect cognitive decline in people with high cognitive functioning.

Benzodiazepine Medication Use

The exposure included benzodiazepines and nonbenzodiazepine hypnotics that bind to the gamma-aminobutyric acid (GABA) receptor such as zolpidem, zaleplon and eszopiclone. These latter medications were used by very few participants. Medication use was ascertained from Group Health computerized pharmacy data that included drug name, strength, route of administration, date dispensed, and amount dispensed.

Studies have not delineated what pattern of benzodiazepine exposure might be important for increasing risk of dementia (e.g. long-term sustained use versus several episodes of periodic use). We hypothesized that cumulative medication 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 benzodiazepine use might effect dementia risk. Therefore, we 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 medication 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).[24] For each participant, we summed the SDDs for all benzodiazepine pharmacy fills during the 10-year exposure window to create a cumulative total standardized daily dose (TSDD).[25-27] We constructed a time-varying measure defined as the TSDD dispensed over a 10-year window after excluding dispensings in

the most recent 1 year, which could have been for prodromal dementia symptoms.[28] Figure 2 illustrates 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 excluding the 1 year immediately prior). We categorized cumulative use as no use, 1to 30 TSDDs, 31 to 120 TSDDs, or 121+ TSDDs based on the distribution of the exposure and clinically meaningful cut-points. 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, triazolam 0.125 mg or lorazepam 2 mg. 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 cognitive trajectory analyses differed in a few ways from the one we defined for dementia analyses. First, cumulative benzodiazepine use was calculated in the 10 years immediately prior to each study visit (i.e. no 1 year-lag) since we were evaluating cognitive decline only in participants who had not yet been diagnosed with dementia. Second, we created a measure of recent use defined as filling two or more benzodiazepine prescriptions in the 6 months prior to each visit, requiring each fill to have at least 7 TSDDs (Figure 2).

Covariates

Information about covariates came from standardized questionnaires administered at each study visit and from Group Health electronic databases. Demographic factors included age, sex, and years of education. Body mass index was determined from measured height and weight.[29] Participants were asked about smoking, exercise and self-rated health.[30] We ascertained presence of several comorbidities including medication-treated hypertension and diabetes mellitus (computerized pharmacy data), history of stroke (self-report or electronic databases),

and coronary heart disease (self-report). Depressive symptoms were obtained from the short version of the Center for Epidemiologic Studies Depression scale.[31]

Statistical Analyses

Dementia and Alzheimer's disease Analyses

We used separate multivariable Cox proportional hazards models with participant's age as the time scale to estimate hazard ratios (HR) and 95% confidence intervals (CI) 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 dementia onset, Group Health disenrollment, or last study visit before September 30, 2012. We adjusted for age at study entry, sex, educational level, hypertension, diabetes mellitus, current smoking, stroke, coronary heart disease, body mass index, regular exercise, self-rated health, and depressive symptoms (variables defined in Table 2). We included time-varying measures for coronary heart 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.

Cognitive Trajectory Analyses

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.[32] 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 (6 months prior to visit) also adjusted for cumulative use (6 months to 10 years prior to visit).

Sensitivity Analyses

For the dementia analyses, we performed several sensitivity analyses to explore the robustness of our results. Given the uncertainty regarding when prodromal symptoms may first emerge prior to a dementia diagnosis, we extended the lag-time to 2 years. In additional models, we included depressive symptoms as a time-varying covariate, and adjusted for the Charlson comorbidity index.[33] Lastly, we performed a post-hoc analysis extending the lag-time to 5 years to replicate the methods used by another study.[9]

All analyses were performed using 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 provides participant characteristics overall and by cumulative benzodiazepine exposure in the 10 years prior to study entry. The median age of participants at study entry was 74, 91% (n=3134) were white, 60% were female, and most (66%) had some college education. Overall, 30% had at least 1 fill for a benzodiazepine in the 10 years before study entry, however

only 2.9% (n=98) had recent benzodiazepine use (within 6 months). Participants with heavier benzodiazepine use were more likely to be female and report fair or poor self-rated health, have higher depressive symptoms and have comorbidities (e.g. 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 82.5% of the benzodiazepine exposure. Within the highest benzodiazepine category (>120 TSDDs), the median level of use was 375 TSDDs (equivalent to slightly over one year of daily use).

Dementia and Alzheimer's disease

The 3,434 participants included in these analyses accrued 25,068 person-years of follow-up, with a mean (SD) of 7.3 (4.8) years. During this time, 797 (23.2%) participants developed incident dementia, of whom 637 (79.9%) developed incident Alzheimer's disease. Table 4 displays the follow-up time and number of events according to exposure status. Figures 3A and 3B show age-adjusted and multivariable adjusted HRs for dementia and Alzheimer's disease associated with cumulative benzodiazepine use. No association was found with the highest level of benzodiazepine use (>120 TSDDs) for dementia (HR 1.07 95% CI 0.83 to 1.37) or Alzheimer's disease (HR 0.95 95% CI 0.71-1.27), compared to non-use. Relative to non-use, a slightly increased risk for dementia was noted for participants with low (1 to 30 TSDDs; HR 1.25, 95% CI 1.03 to 1.51) or moderate use (31 to 120 TSDDs; HR 1.31, 95% CI 1.00 to 1.71); whereas for Alzheimer's disease, increased risk was noted only among participants with low use (HR 1.27; 95% CI 1.03 to 1.57). When we extended the lag-time to 2 years, the associations for the lowest level of benzodiazepine use were no longer statistically significant for either dementia (HR 1.18; 95% CI 0.97 to1.44) or Alzheimer's disease (HR 1.18; 95% CI 0.95 to1.47).

Adjustment for depressive symptoms as a time-varying covariate or for overall comorbidity did not alter estimates appreciably.

Figure 4 shows results from additional analyses that modeled benzodiazepine exposure as a continuous variable using natural cubic splines. These curves show the estimated HRs (and 95% CIs) for each level of exposure relative to a referent group with cumulative exposure of 0 TSDDs. For dementia (Figure 4A), a modestly elevated HR between 1.1 and 1.4 was observed with 90 or fewer TSDDs but risk declines toward 1.0 with higher exposure. Benzodiazepine use was not significantly associated with Alzheimer's disease at any exposure level (Figure 4B). In the post-hoc analysis with a 5-year lag, we continued to find no association between cumulative benzodiazepine use and dementia (Table 5).

Cognitive Trajectory

The average CASI score at baseline was 93.4 (SD 4.7) with similar scores across levels of cumulative benzodiazepine use (range 93.0 to 93.6). No statistically significant differences were found for any benzodiazepine use group in mean CASI or rates of decline compared with non-users (Tables 6 and 7). Those in the highest benzodiazepine use group had 0.002 points slower decline per year compared with people not using benzodiazepines (95% CI, -0.05 to 0.06). There were also no differences in rates of cognitive decline between recent and non-recent users of benzodiazepines (adjusted coefficient, -0.0061; 95% CI, -0.08 to 0.07). Similar results were observed when using the CASI-IRT scores.

DISCUSSION

In this population-based, longitudinal study of older adults, we did not find an 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 (i.e. up to 1

month) or moderate (i.e. 1 to 4 months) benzodiazepine use. This pattern does not support a causal association between cumulative benzodiazepine use and dementia risk, and the small increased risk observed with low use may represent treatment of prodromal symptoms, as supported by our sensitivity analyses. It is also possible that people with prodromal dementia, even years before diagnosis, may be more sensitive to benzodiazepine-induced acute cognitive adverse events (e.g., delirium), resulting in medication discontinuation and avoidance, in turn leading to low levels of use.

Comparison with Other Studies

Of the studies that employed strategies to address reverse causation, our findings are in line with one recent study[14] but are in contrast with two previous studies that reported an increased risk of dementia with benzodiazepine use.[8,9] 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 for developing Alzheimer's disease after accounting for use initated in the prodromal phase. In fact, people who filled more than 100 benzodiazepine prescriptions had a lower risk for Alzheimer's disease than did nonusers, 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 dementia risk (HR 1.62, 1.08 to 2.43).[8] In regard to this latter study, our results are not directly comparable because of differences in study design (i.e. they employed a new user design) and method of ascertaining benzodiazepine use (i.e. they relied on periodic interviews and lacked information about dose, duration or chronicity of use). This 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 residing in Quebec, benzodiazepine use as assessed by computerized pharmacy data 5 to 10 years prior to the index date was associated with increased Alzheimer's disease risk.[9] These authors reported a dose response relationship with no association found for a cumulative dose of less than 91 prescribed daily doses, but increased risk observed for 91 to 180 prescribed daily doses (HR 1.32; 1.01 to1.74) and >180 prescribed daily doses (HR 1.84; 1.62 to 2.08). After adjusting for depression, anxiety and insomnia diagnoses, estimated effects were slightly attenuated, and only the highest use category remained significantly associated with Alzheimer's disease risk.

It is unclear why our findings differ from the Canadian study, but we offer a few possible explanations. Our participants may 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 use in our study fell below the threshold needed to increase dementia risk. 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 a 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 Alzheimer's disease cases; therefore, detection of Alzheimer's disease may be delayed compared to 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 may have more frequent contact with the health care system which

could result in a higher likelihood of dementia being recognized and coded. While we cannot entirely rule out a moderate association in our highest benzodiazepine use group, the confidence limits exclude an association of the magnitude reported in the Canadian study.

Some of the challenges inherent to using an observational study design to examine benzodiazepine use and dementia risk have been discussed, such as accounting for use of these medications to treat prodromal symptoms and limitations to using administrative data for outcome ascertainment. Another methodological challenge is balancing the possible advantages of a new user design with the reality of how people use benzodiazepines (ie. potentially episodic use over several decades) and sample size considerations. A new user design is one strategy to address the bias caused by depletion of susceptible users; however, it is not clear that this design is well suited to examine the principal hypothesis that heavier exposure (e.g., as might be accumulated over many years) is important for increasing dementia risk. Such a design would be challenging to implement in association with prospective follow up of a cohort with a rigorous process for ascertainment of dementia outcomes such as that used in our study, thus forcing the "new user" study to rely on a less optimal outcome definition such as diagnosis codes from administrative or automated data. Additionally, benzodiazepines may be used sporadically over long periods of time on an as-needed basis which could make it challenging to identify true “new users”, particularly in an elderly cohort. A prior study that attempted to identify new users in fact had limited data about benzodiazepine use prior to study enrollment, and so their apparent “new users” may in fact have had a history of benzodiazepine use, suggesting that even this study could have suffered from bias due to depletion of susceptibles.[8]

Strengths and Limitations

Our study has a number of strengths including a large community-based sample, an average follow-up of more than 7 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 study entry and throughout follow-up which to our knowledge is the longest duration used by any study to date for capturing benzodiazepine use. In addition, we were able to examine whether risk varies according to the extent of cumulative use. We specifically designed our study to take into consideration reverse causation and conducted multiple sensitivity and post-hoc analyses to explore the impact of different choices related to defining exposure. Lastly, a strength of this study is the covariate information collected directly from participants about characteristics that are not well measured in administrative data (e.g. physical activity; universal and standardized assessment of depression). A corresponding limitation, however, is that no data on these characteristics are available prior to study enrollment, and thus in some cases, covariates were assessed after the start of exposure. If these confounders lie in the causal pathway, this could result in overadjustment. For many of our covariates, we are not aware of evidence to suggest they may be consequences of (rather than predictors of) benzodiazepine use (e.g. hypertension, diabetes, coronary artery disease). In addition, our point estimates for the adjusted models were not considerably different than the age adjusted models, suggesting that the impact if any of such overadjustment was small.

A few limitations are worth mentioning. We had few participants with very heavy benzodiazepine use, and overall, our participants may have had lower levels of exposure than in some other studies. Like other studies that have examined benzodiazepine use and dementia risk,

we are unable to rule out depletion of susceptible bias. The non-user group may include individuals with past benzodiazepine use who had experienced acute cognitive adverse events because of underlying preclinical dementia pathology, and therefore did not have the opportunity to accumulate higher benzodiazepine use. Other studies suffer from this limitation as well and therefore this potential bias does not explain the differences in study results.[8,9] We are unable to exclude the possibility that within the source population, the most susceptible users of benzodiazepines may have developed dementia at a younger age and therefore been ineligible for study enrollment, which may have biased our findings toward not finding an association. We defined our exposure groups using a 10 year exposure window, and our highest group is likely to include heterogeneous exposure patterns (mix of chronic and intermittent users). Likewise, prior studies have not described or examined patterns of benzodiazpine use.[8,9] Other designs would be necessary to try to address whether the specific pattern of benzodiazepine use is important for dementia risk.

The nature of the association between neuropsychiatric symptoms (e.g. depression, insomnia and anxiety) and dementia risk is unclear and may depend on the timing of the symptoms in relation to the diagnosis. These symptoms occurring in the years just prior to the diagnosis of dementia likely represent prodromal symptoms, however, these same symptoms occurring decades or more prior to the diagnosis may represent risk factors.[34-36] We addressed the possibility of benzodiazepine use for prodromal symptoms in our analysis, however, we were not able to adjust for anxiety and insomnia as risk factors. We did adjust for depressive symptoms which are strongly correlated with anxiety. Results from a prior study suggest that adjustment for anxiety and insomnia are unlikely to considerably alter our findings,[9] and if anything it would be expected to move our HR closer towards the null. We were unable to

ascertain whether prescribers had discontinued benzodiazepines because they identified that a participant had cognitive changes (e.g. delirium) while taking therapy, which may have limited our ability to examine benzodiazepine use and cognitive trajectories. Furthermore, the CASI is a screening tool, making it relatively insensitive to detect cognitive decline in people with high cognitive functioning. However, we still did not find an association between benzodiazepine use and cognitive decline when using methods to overcome this limitation by using the transformed CASI scores. Lastly, most participants were white and relatively well-educated, and so our results may not be generalizable to other groups.

Clinical Implications and Conclusions

In conclusion, we found a slightly higher dementia risk in people with the lowest benzodiazepine use but no elevated risk in those with the highest level of exposure (median exposure equivalent to about 1 year of daily use). Overall, our pattern of findings with cumulative exposure does not support that benzodiazepine use is causally related to increased risk for dementia or cognitive decline. It should be noted that our study did not address the acute cognitive adverse events that can occur with initiating a benzodiazepine in older adults and careful monitoring is recommended in this situation. Although benzodiazepines have been associated with many adverse health outcomes in older adults, our findings from a study using detailed pharmacy data and rigorous outcome assessment suggest that increased dementia risk may not be one of them. Health care providers are still advised to limit benzodiazepine use in older adults to avoid significant adverse events, withdrawal and dependence.

What is already known on this topic

- Benzodiazepine use is common among older adults to manage sleep, anxiety and depressive disorders.
- Studies suggest that benzodiazepine use may be associated with increased dementia risk, although whether this association is causal remains uncertain.

What this study adds

- The highest level of benzodiazepine use was not associated with incident dementia, in contrast to other evidence.
- This study is the first to combine computerized pharmacy data to characterize cumulative benzodiazepine use over a long period (10 years) with rigorous, research based standards used to diagnose dementia and Alzheimer's disease.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that SD received a Merck/American Geriatrics Society New Investigator Award; EB receives royalties from UpToDate; RW received funding as a biostatistician from a research grant awarded to Group Health Research Institute from Pfizer; OY received funding as a biostatistician from research grants awarded to Group Health Research Institute from Amgen and Bayer; and SG, RH, PK, MA have no financial interests that may be relevant to the submitted work.

Authors' contributions: SLG, MLA, SD, RLW, RAH, OY and EBL contributed to study conception and design; all authors contributed to acquisition, analysis, or interpretation of data; SLG and OY drafted the manuscript; all authors revised the manuscript for critical intellectual content; OY conducted statistical analyses; and SD, EBL and PKC obtained funding. SLG and EBL are guarantors.

Ethical approval: The research protocol for this study was approved by the GH and University of Washington institutional review boards. Written informed consent was obtained from all participants.

Access to data: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE LEGEND

Figure 1. Study Sample for Dementia and Cognitive Trajectory Analyses. GH, Group Health.

Figure 2: Scheme for Exposure Definition for Dementia and Cognitive Trajectory Analyses. (A) Defines exposure window for analyses of dementia and Alzheimer's disease. We used a rolling 10-year window to define our time-varying exposures. At each time point during follow-up, the 10 year cumulative exposure for all participants at risk is recalculated by summing all of their benzodiazepine use in the previous 10 years (after excluding the 1 year immediately prior). The measure of cumulative exposure excludes use in the 1 year immediately prior to the event because of concerns about possible use for prodromal symptoms (area shaded in gray). (B) Defines exposure for analyses of cognitive trajectory. The circle at the far right represents a study visit at which the cognitive test was administered. Here, the 1 year immediately prior to a study visit is not excluded from the cumulative use measure because by design, no participants could have been diagnosed with dementia at the time of a study visit included in these analyses. Recent exposure is defined as use in the 6 months immediately before the event.

Figure 3: Association of Cumulative Benzodiazepine Use and Risk of Incident Dementia or Alzheimer's disease. These figures show the HR for all-cause dementia (A) and Alzheimer's disease (B) for each level of cumulative benzodiazepine exposure compared to no use. The triangles represent the age-adjusted HR. The black circles represent HR from the multivariable model adjusted for Adult Changes in Thought study cohort, age at study entry, sex, educational level, hypertension, diabetes mellitus, current smoking, stroke, coronary heart disease, body mass index, regular exercise, self-rated health, and depressive symptoms. The squares show the multivariable adjusted HR when the lag time was increased to 2 years (sensitivity analysis). Bars represent 95% confidence intervals.

Figure 4: Association of Cumulative Benzodiazepine Use Modelled as a Spline and Risk of Incident Dementia or Alzheimer's disease

These figures show the HR for all-cause dementia (A) and Alzheimer's disease (B) according to increasing TSDD compared to no use. The model adjusted for Adult Changes in Thought study cohort, age at study entry, sex, educational level, hypertension, diabetes mellitus, current smoking, stroke,

coronary heart disease, body mass index, regular exercise, self-rated health, and depressive symptoms.

The gray shaded area represents 95% confidence intervals.

TSDD, Total Standardized Daily Dose

Table 1. Benzodiazepine Minimum Effective Dose

Benzodiazepine medication	Minimum Effective Dose
Temazepam	15 mg
Diazepam	4 mg
Clonazepam	0.5 mg
Triazolam	0.125 mg
Lorazepam	2 mg
Alprazolam	0.75 ng
Zolpidem	5 mg
Flurazepam	15 mg
Oxazepam	30 mg
Chlordiazepoxide	15 mg
Clorazepate	15 mg
Eszopiclone	1 mg
Zaleplon	5 mg

Table 2: Characteristics of Participants at Study Entry, Overall and by Prior Cumulative Benzodiazepine Use[a]

		Cumulative benzodiazepine use in 10 years prior to study entry (TSDD)			
Baseline characteristics	**All Subjects (n=3434) N (%)**	**None (n=2416) N (%)**	**1-30 (n=492) N (%)**	**31-120 (n=259) N (%)**	**121+ (n=267) N (%)**
Age in years, median (IQR)	74.4 (70, 80)	74.4 (70, 80)	74.2 (70, 79)	74.4 (70, 79)	75.1 (70, 80)
Male	1387 (40.4)	1050 (43.5)	156 (31.7)	94 (36.3)	87(32.6)
Any college education	2279 (66.4)	1589 (65.8)	336 (68.3)	178 (69)	176 (65.9)
Obese	853 (25.4)	602 (25.4)	138 (29.1)	65 (25.7)	48 (18.5)
Current smoker	173 (5)	122 (5.1)	27 (5.5)	12 (4.7)	12 (4.5)
Regular exercise[b]	2453 (71.6)	1739 (72.2)	340 (69.4)	188 (72.6)	186 (69.7)
Fair or poor self-rated health	532 (15.5)	332 (13.8)	95 (19.4)	50 (19.3)	55 (20.6)
Treated hypertension[c]	1662 (48.4)	1109 (45.9)	263 (53.5)	144 (55.6)	146 (54.7)
Treated diabetes mellitis[d]	272 (7.9)	200 (8.3)	45 (9.1)	15 (5.8)	12 (4.5)
History of stroke[e]	221 (6.4)	125 (5.2)	49 (10)	25 (9.7)	22 (8.2)
Coronary heart disease[f]	633 (18.4)	420 (17.4)	99 (20.1)	50 (19.3)	64 (24)
High depressive symptoms[g]	336 (9.9)	204 (8.6)	52 (10.8)	27 (10.7)	53 (20)

TSDD, Total Standardized Daily Dose; IQR, interquartile range

[a]Column percentages are based on non-missing data. Missing data for each variable: education (n=1), body mass index (n=75), smoking (n=7), exercise (n=8), self-rated health (n=5), depressive symptoms (n=56).

[b]≥15min of activity at least three times a week

[c] Two or more fills in computerized pharmacy data for antihypertensive medications in the year prior to study enrollment

[d] One fill in computerized pharmacy data for an oral hypoglycemic medication or insulin in the year prior to study enrollment

[e] Self-report or codes 430.X, 431.X, 432.X, 434.X, 436.X and 438.X from the *International Classification of Diseases, Ninth Revision*.

[f] Self-reported history of heart attack, angina, angioplasty, or coronary artery bypass surgery

[g] Modified version of the Center for Epidemiologic Studies Depression (CES-D) score of 10 or greater

Table 3. Any and Cumulative Benzodiazepine Use During Study Period [a]

	All participants (N=3434) [b]	TSDD
Benzodiazepine	N (%)	Total TSSD 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

[a] A participant's study period included 10 years prior to study entry through the time they were diagnosed with dementia or censored. We summed TSDD for all participants for their entire study period.

[b] Number of participants with at least 1 fill for a medication in the category at any time during the follow-up period. Participants may have fills for multiple benzodiazepines, so the percentages do not sum to 100%.

Table 4: Follow-up Time and Number of Events According to Exposure Status

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

Table 5. Association of Incident Dementia and Alzheimer's Disease with 6-year Cumulative Benzodiazepine Use With 5-Year Lag Time[a,b]

TSDD[c]	Adjusted Model[d] HR (95% CI)
Dementia	
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	
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; HR Hazard Ratio; CI Confidence Interval; ACT Adult Changes in Thought

[a]Observations with missing adjustment variables are excluded from the model (n=130; 3.8%).

[b]Prescriptions in the 5 years prior to dementia onset were excluded from the calculation of exposure

[c]TSDD example; the minimum effective daily dose for temazepam is 15 mg daily (=1 TSDD); a person would fall into the 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+)

[d]Adjusted for ACT cohort, age (via the time-axis), age at ACT study entry, sex, educational level, body mass index, current smoking, regular exercise, self-rated health, hypertension, diabetes mellitus, stroke, coronary heart disease, history of high depressive symptoms.

Table 6. Difference in Mean Cognitive Scores by Levels of Cumulative Benzodiazepine Use[a,b]

	CASI		CASI-IRT[c]	
	Age-adjusted (95% CI)	Multivariable adjusted (95% CI)[d]	Age-adjusted (95% CI)	Multivariable adjusted (95% CI)[d]
Non-use	Referent	Referent	Referent	Referent
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)
>120	-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)

CASI Cognitive Abilities Screening Instrument; IRT Item Response Theory; TSDD, Total Standardized Daily Dose; CI, Confidence Intervals; ACT, Adult Changes in Thought

[a]Linear regression with generalized estimating equations to account for repeated observations per participant

[b]Negative values mean the exposure category had a lower mean CASI than the reference group. For example, those in the highest benzodiazepine group had a mean adjusted CASI score that was .17 points lower than the non-user group.

[c]The CASI-IRT had a mean score of 0 and a standard deviation (SD) of 1 among individuals without dementia at their most recent study visit.

[d]Model adjusted for ACT cohort, age at study entry, sex, education, hypertension, diabetes, current smoking, stroke, coronary heart disease, body mass index, regular exercise, self-rated health, and depressive symptoms.

Table 7. Difference in Rate of Change by Levels of Cumulative Benzodiazepine Use[a,b]

	CASI		CASI-IRT[c]	
	Age-adjusted (95% CI)	Multivariable adjusted (95% CI)[d]	Age-adjusted (95% CI)	Multivariable adjusted (95% CI)[d]
Non-use	Referent	Referent	Referent	Referent
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)
>120	-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)

CASI Cognitive Abilities Screening Instrument; IRT Item Response Theory; TSDD, Total Standardized Daily Dose; CI, Confidence Intervals; ACT, Adult Changes in Thought

[a]Linear regression with generalized estimating equations to account for repeated observations per participant

[b]Positive values mean the exposure category had a slower decline with age than the reference group.

[c]The CASI-IRT had a mean score of 0 and a standard deviation (SD) of 1 among individuals without dementia at their most recent study visit.

[d]Model adjusted for ACT cohort, age at study entry, sex, education, hypertension, diabetes, current smoking, stroke, coronary heart disease, body mass index, regular exercise, self-rated health, and depressive symptoms.

Figure 1. Study Sample for Dementia and Cognitive Trajectory Analyses

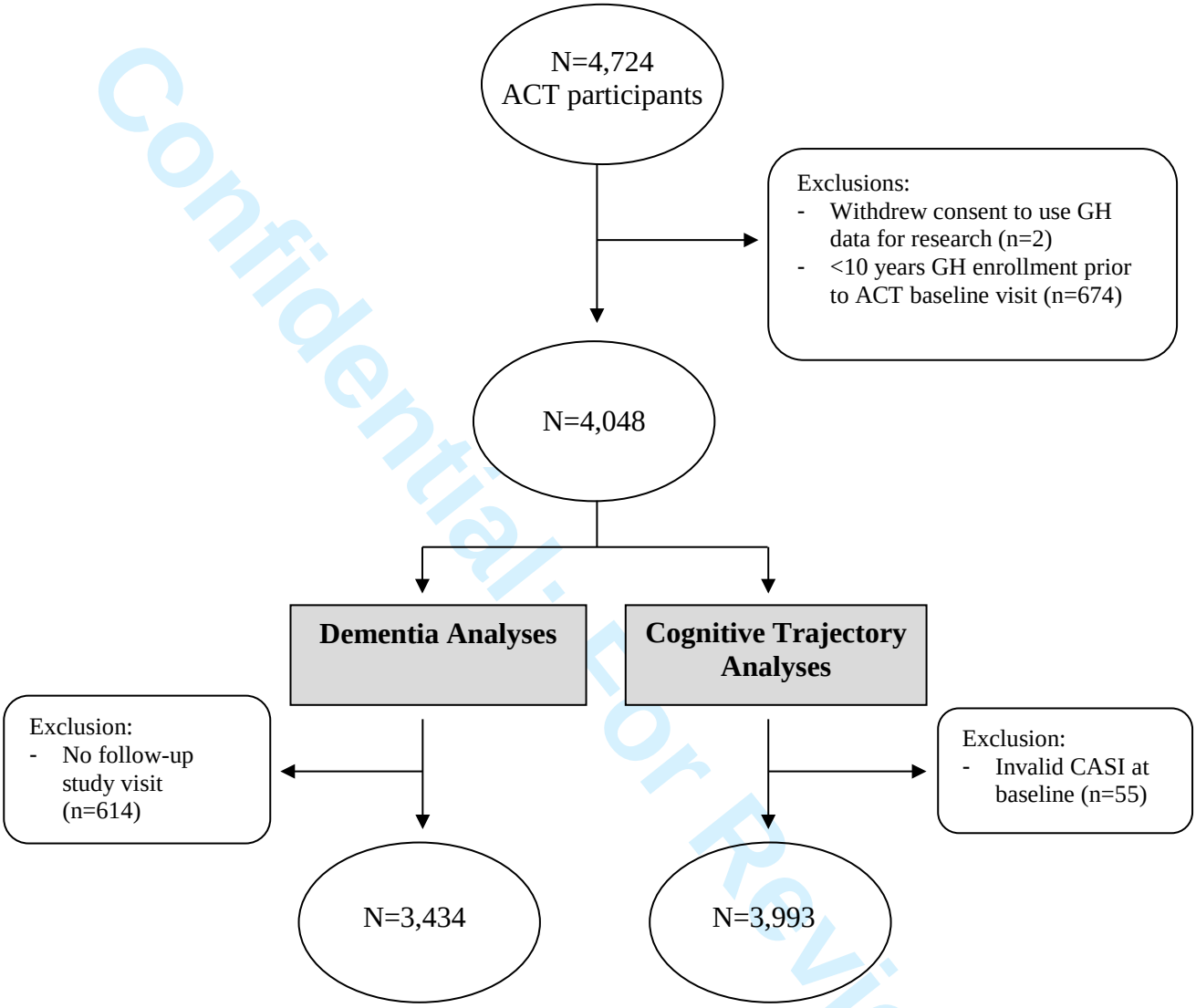


Figure 2: Scheme for Exposure Definition for Dementia and Cognitive Trajectory Analyses

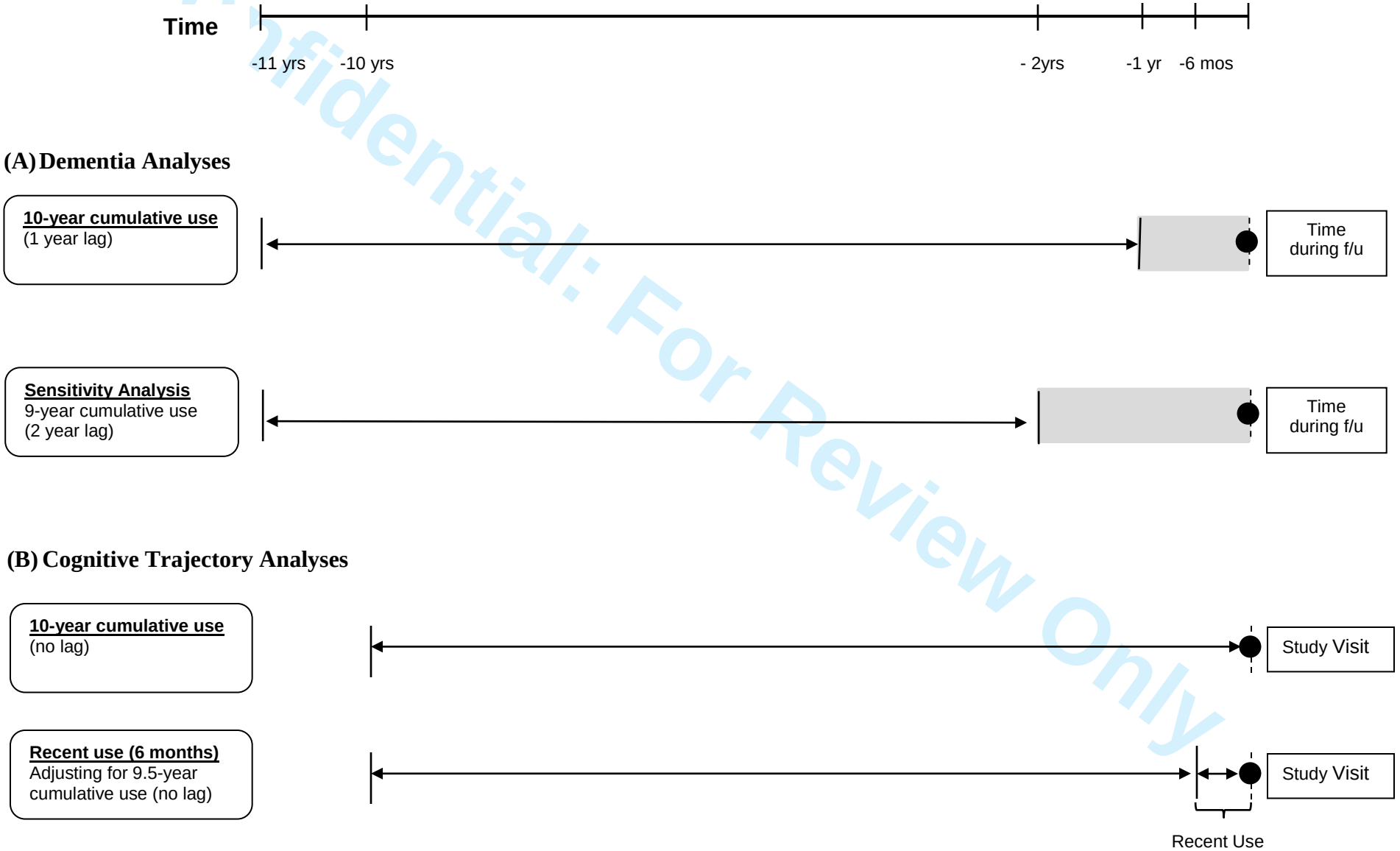


Figure 3: Association of Cumulative Benzodiazepine Use and Risk of Incident Dementia or Alzheimer's Disease

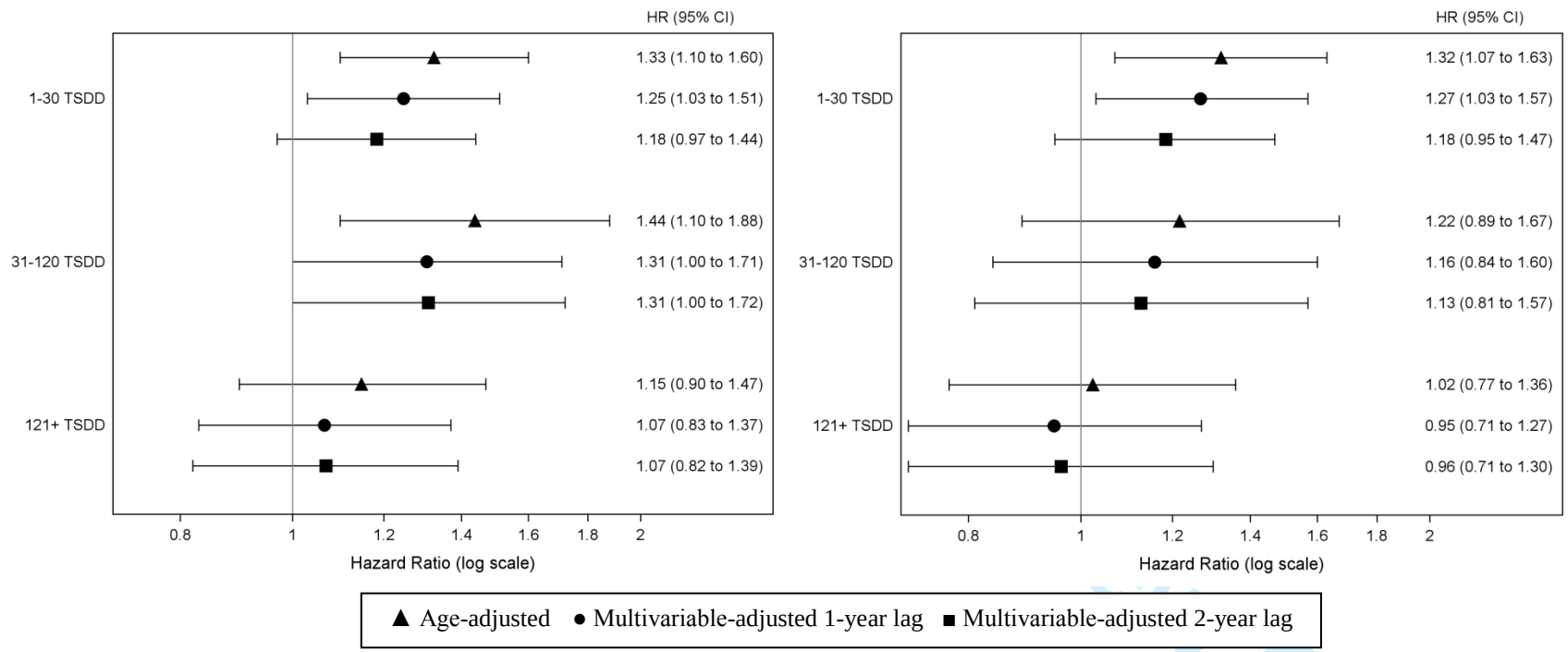
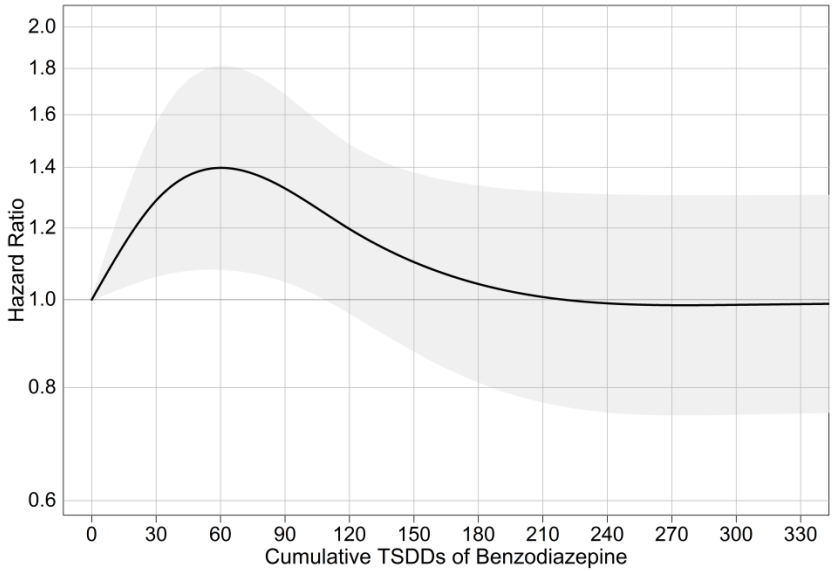


Figure 4: Association of Cumulative Benzodiazepine Use Modelled as a Spline and Risk of Incident Dementia or Alzheimer's disease

(A) Dementia



(B) Alzheimer's disease