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Benzodiazepine use and risk of incident MCI and dementia in a community sample

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Abstract

Objectives: Older adults commonly take benzodiazepines (BZDs) that may have long-term adverse cognitive effects. We investigated whether BZD use was related to developing mild cognitive impairment (MCI) or dementia in cognitively normal older adults in the community.

Setting/Participants: A population-based cohort ($n = 1959$) of adults aged 65 and over, recruited from communities of low socioeconomic status.

Measurements: BZD use, Clinical Dementia Rating (CDR), anxiety symptoms, depression symptoms, sleep difficulties, and *APOE* genotype.

Design: We examined time from study entry to MCI (CDR = 0.5) and time from study entry to dementia (CDR $\geq$ 1) in participants who were cognitively normal at baseline (CDR = 0). We used survival analysis (Cox model), adjusted for age, sex, education, sleep, anxiety, and depression. For all the models, we included an interaction term between BZD use and *APOE*4*.

Results: Taking BZDs was significantly associated with higher risk of developing MCI, but not of developing dementia. The effect was not affected by *APOE* genotype.

Conclusions: In a population-based sample of cognitively normal older adults, BZD use is associated with developing MCI, but not dementia. BZD use may be a potentially modifiable risk factor for MCI.

Key words: anti-anxiety agents, aging, epidemiology

Introduction

People with mild cognitive impairment (MCI) represent a heterogeneous group in the community at large. Compared to those with normal cognition, they are at elevated risk for developing dementia. However, at the population level, only a minority of people with MCI progress to dementia (Ganguli *et al.*, 2019; Hu *et al.*, 2017; Mitchell and Shiri-Feshki, 2009), while the rest remain mildly impaired or even revert to normal. We previously reported that our study participants with MCI who did not progress to dementia reported taking more prescription medications than those who remained normal. Although we attributed that finding to their greater medical comorbidity causing non-progressive cognitive impairment, it also raised the question of whether certain medication groups might elevate the risk of MCI and dementia.

Among older adults, benzodiazepines (BZD) have long been known to be associated with the risk of short-term cognitive impairment and falls. There remains controversy, however, regarding whether they carry risk for long-term, progressive cognitive impairment. The literature focusing on BZDs and risk of MCI or dementia includes studies in different types of cohorts with different research methodology and different findings. Three meta-analyses and a systematic review of reviews show a relationship between BZD

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prescriptions and later development of cognitive impairment (Ferreira *et al.*, 2022; Lucchetta *et al.*, 2018; Mitra, 2022; Penninkilampi and Eslick, 2018). However, a different systematic review did not show evidence of a relationship between long-term BZD use and cognitive decline (Nader and Gowing, 2020). Importantly, few studies in the literature use population-based research samples, and fewer still look at incidence of both MCI and dementia.

Though frequently shown to be effective in the short-term, long-term use of BZDs remains both common and controversial (Chiu *et al.*, 2021; Curran *et al.*, 2003; Goddard *et al.*, 2001; Hata *et al.*, 2018). It would be of great help to clinicians to know whether BZDs increase the risk for either reversible or progressive cognitive impairment. In the current work, we examine a population-based cohort of older adults to determine whether there is evidence for increased risk of MCI or dementia among BZD users.

Methods

Study participants

We recruited our study cohort, called the Monongahela-Youghiogheny Health Aging Team (MYHAT), from small towns in southwestern Pennsylvania, a Rust Belt region of relatively low socioeconomic status. The overarching focus of the MYHAT study is the epidemiology of MCI. The MYHAT cohort is an age-stratified, random sample recruited from voter registration lists. Enrollment occurred between 2006 and 2008. Participants were included if they were 65 years old and older, were living in the selected region, were community dwelling (not in long-term care), were able to participate in neuropsychological testing (including having relatively intact hearing and vision), and had decisional capacity (Ganguli *et al.*, 2010; Ganguli *et al.*, 2019). We obtained informed consent from 2036 people. Since the larger study aims were to identify people at risk for developing MCI or dementia, we screened everyone using the age-education-corrected mini-mental state examination (MMSE) (Folstein *et al.*, 1975; Mungas *et al.*, 1996) and excluded those with age-education corrected MMSE scores less than 21 at the time of study enrollment. We gave the full baseline assessment to 1982 individuals and requested to repeat the assessment annually. The University of Pittsburgh Institutional Research Board approved all study procedures for the protection of human subjects, and all participants provided written informed consent at the study entry.

Demographic

Demographic data were collected at baseline and included age, sex, and education (less than high school, high school, and greater than high school).

BZD use

At each visit, participants were requested to show interviewers all the prescription and non-prescription medications and supplements that they were currently taking. Medication data were transcribed from bottle labels and then entered by brand and generic names as well as according to therapeutic category based on the American Hospital Formulary System. BZDs were identified in the database and used in these analyses.

To address confounding by indication, we adjusted our analytic models for the conditions for which BZDs are most commonly prescribed: depressive symptoms, anxiety symptoms, and sleep difficulties.

Depressive symptoms

Depression symptoms were assessed using the 20-item modified Center for Epidemiologic Studies – Depression scale (mCES-D), using a 90th percentile score in this MYHAT cohort as the cutoff (Ganguli *et al.*, 1995; Radloff, 1977).

Anxiety symptoms

Anxiety symptoms were obtained at each follow-up assessment based on two questions to screen for anxiety symptoms: (1) "Would you describe yourself as a worrier?" and (2) "Would you say that you easily become nervous or upset?" Question 2 was asked only if participants responded positively to question 1. These two questions are generalized anxiety disorder screening questions from the Penn State Worry Questionnaire (Andreescu *et al.*, 2014; Brown *et al.*, 1992). We categorized participants as "worry" if they responded positively to question 1 but negatively to question 2, and we categorized participants as "generalized anxiety" if they responded affirmatively to both questions 1 and 2.

Sleep complaints

Sleep complaints were assessed annually based on participants responding affirmatively to two questions about difficulty falling asleep and difficulty staying asleep.

APOE genotype

We also adjusted our models for the *APOE*4* genotype, which is a well-established risk factor for

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cognitive decline, MCI, and dementia in older adults (Ganguli *et al.*, 2014; Qian *et al.*, 2017). Genotyping was carried out on blood or saliva specimens provided by study participants.

MCI and dementia rating

Each participant was assessed using the Clinical Dementia Rating (CDR®) Dementia Staging Instrument (Morris, 1993) by trained interviewers at baseline and each annual follow-up visit, based on evaluating everyday functioning across cognitively driven functional domains. CDR $\geq$ 1.0 was defined as dementia, and CDR = 0.5 was defined as MCI. For analyses with dementia as an outcome, those with CDR = 0 or CDR = 0.5 at the beginning of the study were included. For analyses using MCI as an outcome, only those with CDR = 0 were included.

Statistical analyses

At baseline, the continuous variable age was presented as mean (SD); frequencies with percentages were calculated for sex, educational level (less than high school, high school, more than high school), depression symptoms (mCES-D $\geq$ 5, mCES-D < 5), sleep complaints, anxiety symptoms, and BZD use. For between group comparison (BZD users vs non-users), chi-squared test was conducted for categorical variables and *t*-test was conducted for continuous variables.

Separate multivariable Cox proportional hazards models were used to assess whether BZD use was associated with the risk of developing MCI and dementia. Time to MCI was calculated as time (in years) from baseline (cycle 1) to the cycle that the participant was first rated CDR = 0.5, and time to dementia was calculated as time (in years) from baseline (cycle 1) to the cycle that the participant was first rated CDR $\geq$ 1. Observations were censored if dropout was observed prior to observing CDR = 0.5 (for time to MCI) or CDR >= $\geq$ 1 (for time to dementia). We adjusted for the following covariates in the model: age, sex, education, sleep difficulties (difficulty falling asleep, difficulty staying asleep), anxiety symptoms (worry, generalized anxiety), and depression symptoms (mCES-D). All covariates except sex and education were treated as time-varying covariates. Thus, these models take into account BZD use at all assessment waves, regardless of the number of waves at which a given participant reported taking them. We also fit Cox models to assess if the association between BZD use and risk of developing MCI and dementia were moderated by the *APOE*4* genotype by including an interaction term between BZD use and *APOE*4*. We calculated the adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs) and the corresponding *p*-values. The proportional hazards assumption was assessed using the Schoenfeld residuals. All statistical analyses were conducted using R statistical package, version 3.6.3 (R-Core-Team, 2020).

Results

Baseline characteristics

Over the course of the study, the cohort (N = 1,959, excluding 23 participants who already had CDR $\geq$ 1 at baseline) experienced 81% attrition with 373 participants remaining in the study at the 13-year point. The median length of follow-up was 5.1 years (quartiles 2.0, 5.1, 10.1). At study entry/baseline, 1,959 participants were dementia free (CDR < 1), but 4 of them did not provide baseline medication information. Among the remaining 1,955 participants (Table 1), their mean (SD) age was 77.6 (7.4) years, and 61.3% were women; 13.5%, 45.2%, and 41.3% had education less than high school, equal to high school, and greater than high school, respectively, and 7.7% participants took BZDs. Sleep difficulties and anxiety symptoms were significantly more common in those who took BZDs. While age was not significantly associated with BZD use, women were more likely to take BZDs than men. Participants with high school education were more likely to take BZDs than those with less than high school education or greater than high school education.

Progression to MCI and dementia

Among the individuals included in these analyses, during the period that we observed them, 135 individuals progressed from MCI (CDR = 0.5) to dementia (CDR $\geq$ 1); 63 of them went from normal (CDR = 0) through MCI to dementia.

Association between BZD use and developing MCI

During follow-up, 405 participants developed MCI. The multivariable Cox model showed that BZD use was significantly associated with a 50% higher risk of developing MCI among those who took BZDs as compared to those who did not, adjusting for age, sex, education, depression symptoms, sleep complaints, and anxiety symptoms (Table 2). For the association between *APOE*4* and MCI, the HR was 1.6 (95% CI 1.2–2.0), $p < 0.001$. However, the interaction between BZD and *APOE*4* was not significantly associated with MCI (HR = 0.8 (0.3, 1.7)), $p = 0.51$. This indicates that the association between BZD use and the risk of developing MCI was not significantly different between people with and without APOE*4.

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Table 1. Baseline characteristics by any BZD use

	ALL ($N = 1,955$)	ANY BZD USE: NO ($N = 1,805$)	ANY BZD USE: YES ($N = 150$)	TEST STATISTICS	DF	P VALUE
Age	77.6 (7.4)	77.7 (7.4)	76.6 (7.7)	1.6	172.4	0.104*
Female	1198 (61.3%)	1087 (60.2%)	111 (74.0%)	10.5	1	0.001**
Education				14.3	2	0.001**
<high school	264 (13.5%)	245 (13.6%)	19 (12.7%)			
=high school	883 (45.2%)	794 (44.0%)	89 (59.3%)			
>high school	808 (41.3%)	766 (42.4%)	42 (28.0%)			
mCES-D ≥ 5	114 (5.9%)	90 (5.0%)	24 (16.2%)	29.3	1	<0.001**
Difficulty falling asleep	740 (37.9%)	660 (36.6%)	80 (53.3%)	15.8	1	<0.001**
Difficulty staying asleep	799 (40.9%)	721 (40.0%)	78 (52.0%)	7.7	1	0.005**
Worry	324 (16.6%)	290 (16.1%)	34 (22.7%)	3.9	1	0.049**
Generalized anxiety	501 (25.7%)	420 (23.3%)	81 (54.0%)	66.8	1	<0.001**

Table shows mean (SD) or frequency (%). *P*-values were based on two-sample *t* test (*) for continuous variable, and chi-squared test (**) for categorical variables.
Abbreviations: BZD, benzodiazepine; DF, degree of freedom; mCES-D: modified Center for Epidemiologic Studies – Depression scale.

Table 2. Adjusted hazards ratios for taking any BZD on developing MCI or dementia[b]

	MCI OUTCOME		DEMENTIA OUTCOME	
VARIABLE	HR (95% CI)	*p* VALUE[a]	HR (95% CI)	*p* VALUE[a]
Age	1.1 (1.1, 1.1)	<0.001	1.1 (1.1, 1.2)	<0.001
Female	1.1 (0.9, 1.4)	0.333	1.0 (0.7, 1.5)	0.854
Education				
<high school	Reference		Reference	
=high school	0.8 (0.6, 1.0)	0.086	0.7 (0.4, 1.1)	0.120
>high school	0.6 (0.4, 0.8)	0.001	0.6 (0.4, 1.0)	0.054
Difficulty falling asleep	1.0 (0.8, 1.3)	0.973	1.0 (0.7, 1.5)	0.891
Difficulty staying asleep	1.2 (0.9, 1.4)	0.184	0.8 (0.5, 1.2)	0.257
Worry	1.0 (0.7, 1.3)	0.822	1.1 (0.7, 1.8)	0.665
Generalized anxiety	1.1 (0.8, 1.4)	0.653	1.1 (0.7, 1.7)	0.537
mCES-D ≥ 5	2.1 (1.4, 3.2)	<0.001	1.9 (1.0, 3.7)	0.057
Any BZD use	1.5 (1.0, 2.1)	0.028	0.9 (0.5, 1.9)	0.830

[a] A multivariable Cox proportional hazards regression model was fit for each outcome.
[b] MCI and dementia were defined as Clinical Dementia Rating (CDR) score = 0.5 and ≥ 1, respectively.
Abbreviations: BZD, benzodiazepine; CI, confidence interval; mCES-D: modified Center for Epidemiologic Studies – Depression scale; MCI, mild cognitive impairment; HR, hazard ratio.

Association between BZD use and developing dementia

During follow-up, 135 participants developed dementia. The multivariable Cox model shows that BZD use was not significantly associated with higher risk of developing dementia, adjusting for age, sex, education, depression symptoms, sleep complaints, and anxiety symptoms (Table 2). For the association between APOE-4 and dementia, the HR was 2.6 (1.9–3.8), $p < 0.001$. The interaction between BZD use and APOE*4 was not significantly associated with dementia (HR = 0.6 (0.1–3.3)), $p = 0.6$.

Discussion

Our analysis revealed that BZD use was associated with development of MCI, but not dementia, in a population-based sample of older adults from small-town communities in Western Pennsylvania. The association was not driven by indications for BZD prescription; we controlled for "confounding by indication" by including depression, anxiety, and insomnia as covariates in our models. The association was also not driven by *APOE*4* genotype, an established risk factor for MCI and dementia.

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Although we are not aware of other studies that looked specifically at MCI, a few have examined the relationship between cognitive impairment, not dementia (CIND) and BZD use. Two previous population-based studies warrant comparison to the MYHAT study because they used approaches sufficiently like ours. In the Canadian Study of Health and Aging (CSHA), similarly to our study, BZD use was linked with development of CIND and not with dementia (Nafti *et al.*, 2020). In the Caerphilly Prospective Study, the results contrast with our own, showing no relationship between BZD use and CIND but showing increased risk of dementia among BZD users (Gallacher *et al.*, 2012). One reason for the differing findings may be the differing ways of assessing cognitive impairment. CSHA used the results of a neuropsychological battery and then applied ICD-10 criteria to define dementia. By contrast, the Caerphilly Prospective Study categorized individuals as having CIND if they failed their cognitive screen but did not meet criteria for dementia on a neuropsychological battery, which could be a more heterogeneous group. Our own group examined MCI, not CIND, and looked at a functional definition of MCI (CDR = 0.5). In our past work, we have found that a CDR of 0.5 picks up more individuals with MCI than using purely cognitive criteria but is often concurrent with other ways of measuring MCI (Ganguli *et al.*, 2010). An additional distinction between these studies and the work presented here is that we were able to address the risk of confounding by indication by controlling for depressive symptoms, anxiety symptoms, and insomnia at each time point.

Prior research has shown varied results on the relationship between BZDs and dementia in population samples. There have been studies that show relationship, no relationship, or relationship for low exposure users but not for high exposure users (Billioti de Gage *et al.*, 2012; Dyer *et al.*, 2021; Gallacher *et al.*, 2012; Gray *et al.*, 2016; Grossi *et al.*, 2019; Hafdi *et al.*, 2020; Lagnaoui *et al.*, 2008; Shash *et al.*, 2016). Looking at MCI specifically might offer some illumination on these disparate findings. If BZDs impact cognition but do not independently increase risk for progressive dementia, then subtle variations in how cognition is measured and how dementia is diagnosed could lead to disparate results. Intriguingly, a study done in a memory clinic population with amnestic MCI suggested that BZDs were protective against amyloid accumulation (Desmidt *et al.*, 2019). We would hypothesize that this finding might be influenced by using a memory clinic sample with amnestic MCI, who would be higher risk of developing dementia than those with either amnestic or non-amnestic MCI in the population (Hu *et al.*, 2017; Mitchell and Shiri-Feshki, 2009). However, more importantly, their findings suggest that BZDs are not causing cognitive impairment through Alzheimer's pathology. A recent study on rats showed that there was no relationship between BZD use and neurogenesis or apoptosis, though BZD use was shown to impact cellular structure (Furukawa *et al.*, 2021).

Strengths and limitations of our study can be viewed as existing in conversation with each other. It is important to study MCI within population-based samples as these individuals are commonly seen in primary care or mental health clinics but may not present to memory care settings. Because our cohort is representative of the population from which it was drawn, it reflects the demographics of the older adults who reside in the study area. Replication in a more racially and ethnically diverse population would increase the generalizability of the current findings. We had a large population-based cohort whom we assessed annually for cognitive impairment. We used the CDR which is an especially useful tool tied to functional outcomes rather than to cognitive test performance. By measuring MCI, our work provides information that is not obtainable in the studies from around the world that examine the link between BZD use and dementia in health care, insurance, or pharmacy databases, for example (Aldaz *et al.*, 2021; Baek *et al.*, 2020; Gerlach *et al.*, 2021; Gomm *et al.*, 2016; Joyce *et al.*, 2022; Lin *et al.*, 2020). This being an observational study, we do not expect to establish causality. Further, we were able to address confounding by indication by annually assessing symptoms of depression, anxiety, and insomnia, which are not well-captured in pharmacy or claims databases. However, we can only capture these symptoms which are present despite BZD use, i.e., not those which responded favorably to BZDs. We were able to follow our patients for as long as 13 years. The Cox models with time-varying covariates took into account BZD use at all assessment waves, regardless of the number of waves at which a given participant reported taking them. However, these models do not allow us to calculate the hazard associated with taking BZDs a specific number of times. We were able to control for *APOE*4* genotype which is not usually possible in claims databases.

Our findings have relevance to several different sets of stakeholders. Older adults and their physicians have an interest in trying to optimize their cognition. Though we cannot infer causation from our results, our clinical experience is that older adults with concerns about their cognition and current BZD use may benefit from a slow taper. Discussing the relationship between BZD use and

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cognition can increase patient buy-in to deprescribing. Our findings showing BZD use to be associated with MCI but not dementia suggest that BZD use might lead to the subtype of MCI that does not progress to dementia. Should we develop disease-specific interventions that are administered at early stages of cognitive impairment, it will be important to identify sources of cognitive impairment that do not lead to dementia, i.e., potentially modifiable risk factors for MCI. This work indicates that BZD use is one factor to consider when making this determination.

Conflict of interest

None.

Description of authors' roles

Esther G. Teverovsky contributed to the study concept and design, study supervision, interpretation of results, drafting, and critical revision of the manuscript.

Ariel Gildengers contributed to the interpretation of the results and critical revision of the manuscript.

Xinhui Ran contributed to the data analysis, interpretation of the results, drafting, and critical revision of the manuscript.

Erin Jacobsen contributed to the data acquisition and critical revision of the manuscript.

Chung-Chou H. Chang contributed to the data analysis, interpretation of the results, and critical revision of the manuscript.

Mary Ganguli contributed to the study concept and design, study supervision, interpretation of results, drafting, and critical revision of the manuscript.

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