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Hypertension control and risk of age-associated dementia in people with HIV infection

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Objective: Hypertension is a major risk factor for dementia, but sustained blood pressure control is difficult to achieve. We evaluated whether inadequately controlled hypertension may contribute to excess dementia risk among people with HIV.

Design: A retrospective cohort study.

Methods: We studied demographically matched people with and without HIV between July 1, 2013, and December 31, 2021, who were at least 50 years old and had a hypertension diagnosis but no dementia diagnosis. Hypertension control was calculated using a disease management index (DMI), which captured degree and duration above the hypertension treatment goals of SBP less than 140 mmHg and DBP less than 90 mmHg. DMI values ranged from 0 to 100% (perfect control); hypertension was considered 'inadequately controlled' if DMI was less than 80% (i.e., in control for <80% of the time). Annual, time-updated DMI was calculated for SBP and DBP. Associations of SBP and DBP control with incident dementia were evaluated using extended Cox regression models.

Results: The study included 3099 hypertensive people with HIV (mean age: 58.3 years, 90.2% men) and 66 016 people without HIV. Each year of inadequate SBP control was associated with greater dementia risk in both people with HIV (adjusted hazard ratio [aHR] = 1.26, 0.92–1.64) and people without HIV (aHR = 1.27 (1.21–1.33)); *P*-interaction = 0.85). Similarly, inadequate DBP control was associated with greater dementia risk in both people with HIV (aHR = 1.43, 0.90–1.95) and people without HIV (aHR = 1.71, 1.50–1.93; *P*-interaction = 0.57).

Conclusion: Findings suggest the association of inadequate hypertension control with greater dementia risk is similar by HIV status. Stronger associations of DBP control with dementia merit further investigation.

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Introduction

People with HIV infection experience a disproportionately high rate of cognitive impairments compared with the general population [1,2]. Additionally, some studies report increased risk of dementia among people with HIV in older age, even after accounting for sociodemographic factors and comorbidities [3–6]. One potential explanation for the excess dementia risk observed in this population is the impact of vascular comorbidities such as hypertension, which could compound the adverse effects of HIV infection on brain and vascular health [7].

Hypertension is common among people with HIV and is a major modifiable risk factor for dementia [8,9]. Greater attention to blood pressure control may therefore be important to reduce the burden of cognitive impairments as this population ages. Indeed, emerging evidence suggests that cognitive decline among people with HIV receiving antiretroviral therapy is more strongly associated with treatable age-related comorbidities such as hypertension than with chronological age [10]. Although current HIV care guidelines recommend routine blood pressure monitoring and treatment of hypertension [11], sustained hypertension control may be difficult to achieve given competing priorities related to HIV management. The goal of this study was to better understand the relationship between inadequately controlled hypertension and risk of dementia among hypertensive individuals with HIV.

Materials and methods

Study design

We conducted a retrospective cohort study that included hypertensive people with HIV and a comparator group of people without HIV who were members of Kaiser Permanente Northern California (KPNC), an integrated healthcare system in the U.S. KPNC provides comprehensive medical services to a diverse membership of nearly 4.6 million individuals. Adult KPNC members are similar to the underlying insured general population in its service area in terms of age, sex, race/ethnicity, and educational attainment [12].

Individuals were selected from an established cohort of people with and without HIV at least 18 years of age with KPNC membership between July 1, 2013, and December 31, 2021, and who were matched 1:20 on age, sex, race/ethnicity, and duration of KPNC membership [13]. Individuals were included in this analysis if they met the following eligibility criteria: at least 50 years of age, no prior dementia diagnosis, prior hypertension diagnosis (≥ 2 outpatient diagnoses, or 1 outpatient diagnosis and hypertension medications filled), at least 6 months of continuous KPNC membership, and at least two blood

pressure measurements. People with HIV were additionally required to have at least one antiretroviral therapy prescription fill.

Baseline was defined as the date that individuals met all eligibility criteria. Follow-up ended on the first of the following: date of incident dementia, death, end of KPNC membership, or end of the study. The KPNC institutional review board approved this study.

Data sources

Data were drawn from the KPNC electronic health record (EHR) and the KPNC HIV Registry. The HIV Registry includes all known cases of HIV infection in the patient population, with all cases confirmed by chart review.

Hypertension control

Hypertension control was calculated using a disease management index (DMI), which captured the degree and duration above the hypertension treatment goals of SBP less than 140 mmHg and DBP less than 90 mmHg (based on clinical blood pressure targets used during the study period). Methods are described in more detail in the Supplemental material, <http://links.lww.com/QAD/D335> and have also been described previously [13]. Briefly, DMI is computed using all blood pressure values during 6-month periods that are updated monthly; the DMI equation divides the total degree and duration of time above hypertension treatment goals by the total time period of measurement. DMI values ranged from 0 to 100% (perfect control); hypertension was considered 'inadequately controlled' if DMI was less than 80% (i.e., not in control for at least 80% of the time). Annual, time-updated DMI was calculated separately for SBP and DBP.

Dementia

The outcome of interest was incident dementia of any type, identified using International Classification of Diseases (ICD) codes in the EHR [4]. Dementia types included Alzheimer's disease, vascular dementia, Parkinson's dementia, dementia with Lewy bodies, frontotemporal dementia, and other or unspecified dementias.

Covariates

Data were collected from the EHR at baseline on sociodemographic, vascular, and other clinical factors known to be associated with dementia. Sociodemographic factors included age, sex, race, ethnicity, and neighborhood-level socioeconomic status [14]. Vascular factors included history of smoking and ICD-coded diagnoses of cardiovascular disease, cerebrovascular disease, and diabetes. Other dementia-risk factors included obesity (body mass index ≥ 30 kg/m²), and ICD-coded diagnoses of substance use disorders and mental health disorders (depression or anxiety). Data were also collected on health insurance type and number of outpatient and telehealth encounters (measure of healthcare utilization). For people with HIV, descriptive

data were collected on HIV RNA levels, CD4⁺ cell count, HIV risk (i.e., male-to-male sexual contact, heterosexual, injection drug use, other), and known duration of HIV infection.

Statistical analyses

Baseline characteristics of study participants were compared descriptively by HIV status. The cumulative proportions of people who developed dementia during follow-up were compared by HIV status using Kaplan–Meier analysis. Then, the associations of annual, time-updated SBP and DBP control with incident dementia were evaluated in separate extended Cox models with age as the time scale, accounting for dementia risk factors listed in the Methods. HIV-specific factors were not included in the models. The continuous DMI variables were interpreted as the increased risk of dementia per year of inadequately controlled SBP or DBP. Differences in associations by HIV status were evaluated in models which included terms for the interaction of hypertension control and HIV. Analyses were completed using SAS version 9.4.

Results

The study included 3099 people with HIV (mean age: 58.3 years, 90.2% men, 58.7% White, 19.2% Black, 11.7% Hispanic, 4.9% Asian, 5.4% other or unknown race/ethnicity) and 66 016 demographically similar people without HIV (Table 1). All people with HIV were on antiretroviral therapy. At baseline, 93.4% of people with HIV had HIV RNA levels less than 200 copies/ml, 65.1% had CD4⁺ cell counts of at least 500 cells/ μ l, and the mean duration of known HIV infection was 17.7 years. At baseline, SBP was inadequately controlled (DMI <80%) for 8.6% of people with HIV and 10.2% of people without HIV ($P < 0.01$); DBP was inadequately controlled for 4.0% of people with HIV and 4.2% of people without HIV ($P = 0.58$).

Over a mean follow-up of 5 years, the cumulative incidence of dementia at age 85 was 24.9% (95% CI = 15.7–33.1) among people with HIV compared with 17.3% (95% CI = 16.5–18.2) among people without HIV (log rank p -value <0.001). As shown in Fig. 1, each year of inadequately controlled SBP was associated with greater dementia risk in both people with HIV (adjusted hazard ratio [aHR] = 1.26, 0.92–1.64) and people without HIV (aHR = 1.27, 1.21–1.33; P -interaction = 0.85). Similarly, inadequate DBP control was also associated with greater dementia risk in both people with HIV (aHR = 1.43, 0.90–1.95) and people without HIV (aHR = 1.71, 1.50–1.93; P -interaction = 0.57), though the associations of SBP and DBP with dementia among people with HIV did not reach statistical significance.

Discussion

This study contributes novel data on cumulative exposure to inadequately controlled hypertension and its association with dementia risk among people with HIV. Using blood pressure measures collected during routine clinical encounters in a large U.S. healthcare system, we quantified the relationship of inadequately controlled hypertension with incident dementia among hypertensive adults with versus without HIV. During study follow-up, the cumulative proportion of incident dementia by age 85 was greater among people with HIV (25%) versus people without HIV (17%). Inadequate control of both SBP and DBP was associated with higher risk of dementia, and these associations were similar by HIV status. This suggests that while hypertension may play a significant role in dementia risk, worse hypertension control likely does not explain the higher cumulative incidence of dementia among people with HIV.

Overall, our findings indicate that the impacts of uncontrolled hypertension on dementia do not appear to be different by HIV status. Notably, we observed associations of hypertension with dementia even though blood pressure control was overall quite high at baseline for both people with and without HIV, reinforcing the strong impact of hypertension on dementia risk. High levels of blood pressure control have been previously reported at KPNC [13,15,16] and have been attributed to a hypertension control program, which includes prompts in the EHR for monitoring blood pressure and an evidence-based protocol for hypertension management [15,16]. Similar programs in other settings, including safety-net clinics and federally funded health systems, demonstrate similar results [17–19] and emphasize the potential of systems-level programs to increase hypertension awareness and control. However, to some extent, it may have diminished our ability to detect effects of prolonged uncontrolled blood pressure or to distinguish cross-group variability in hypertension control and dementia risk. Potential heterogeneity in associations by population subgroup or HIV severity would be worth investigating in future studies.

An unexpected finding was that the association of DBP control with incident dementia was stronger than the association of SBP control with incident dementia; this was the case for both people with and without HIV. Clinical and research attention has focused primarily on SBP given its strong association with cardiovascular morbidity and mortality. However, our results support examination of both SBP and DBP in relation to dementia risk. The clinical implications of high DBP for cognitive health, including underlying mechanisms by which diastolic hypertension could affect the brain over the life course, are unclear.

A key methodological contribution of this study was quantification of hypertension exposure using longitudinal analysis of blood pressure measures from routine healthcare

Table 1. Study population characteristics at baseline by HIV status.

Characteristic	People with HIV N = 3099 n (%)	People without HIV N = 66 016 n (%)
Age, years		
50–59	1890 (61.0)	38 967 (59.0)
60–69	966 (31.2)	15 851 (24.0)
≥70	243 (7.8)	11 194 (17.0)
Male	2795 (90.2)	59 138 (89.6)
Race and ethnicity		
Asian	152 (4.9)	3637 (5.5)
Black	595 (19.2)	13 220 (20.0)
Hispanic	364 (11.7)	8396 (12.7)
White	1820 (58.7)	38 973 (59.0)
Other or unknown	168 (5.4)	1790 (2.7)
Neighborhood socioeconomic status quartiles		
1 (highest SES)	743 (24.0)	11 666 (17.7)
2	844 (27.2)	21 000 (31.8)
3	798 (25.8)	18 770 (28.4)
4 (lowest SES)	714 (23.0)	14 543 (22.0)
Unknown	0 (0.0)	37 (0.1)
Insurance type		
Commercial	1922 (62.0)	45 097 (68.3)
Medicare	1064 (34.3)	19 560 (29.6)
Medicaid	81 (2.6)	926 (1.4)
Other or unknown	32 (1.0)	433 (0.6)
Obesity (body mass index ≥30 kg/m ²)	862 (27.8)	33 049 (50.1)
Ever smoker	1852 (59.8)	33 536 (50.8)
Substance use disorder	788 (25.4)	9495 (14.4)
Depression or anxiety	1914 (61.8)	23 746 (36.0)
Cardiovascular disease	563 (18.2)	11 751 (17.8)
Cerebrovascular disease	270 (8.7)	5275 (8.0)
Diabetes mellitus	793 (25.6)	18 901 (28.6)
Median SBP (IQR)	129.0 (119.0–137.0)	130.0 (122.0–137.0)
Median DBP (IQR)	77.0 (69.0–84.0)	77.0 (70.0–84.0)
Median duration of KPNC membership, years (IQR)	10.1 (2.8–16.6)	11.9 (3.7–16.6)
Reason for end of follow-up		
Dementia diagnosis	85 (2.7)	2480 (3.8)
Death	233 (7.5)	5239 (7.9)
End of KPNC membership	675 (21.8)	13 242 (20.1)
End of study	2,106 (68.0)	45 055 (68.2)
HIV RNA level (copies/ml)		–
<200	2895 (93.4)	
200–9999	58 (1.9)	
≥10 000	69 (2.2)	
Unknown	77 (2.5)	
CD4 ⁺ cell count (cells/μl)		–
≥500	2016 (65.1)	
200–499	802 (25.9)	
<200	124 (4.0)	
Unknown	157 (5.1)	
HIV risk category		–
Male-to-male sexual contact	2067 (66.7)	
Heterosexual	494 (15.9)	
Injection drug use	236 (7.6)	
Other or unknown	302 (9.8)	
Mean duration of known HIV infection, years (SD)	17.7 (8.6)	–

IQR, interquartile range; KPNC, Kaiser Permanente Northern California; SD, standard deviation; SES, socioeconomic status.

visits [13]. Importantly, we used a time-updated index which was a more robust measure of hypertension exposure than single time-point measurements or cumulative measures calculated over discrete (time-limited) windows. Another novel contribution was evaluation of clinically diagnosed dementia rather than intermediate outcomes along the cognitive decline trajectory such as

changes in cognitive function or diagnosis of mild cognitive impairment. However, dementia is a relatively rare outcome; therefore, the associations of SBP and DBP with dementia among people with HIV did not reach statistical significance and would warrant evaluation in other large cohorts or further study as people with HIV advance in age.

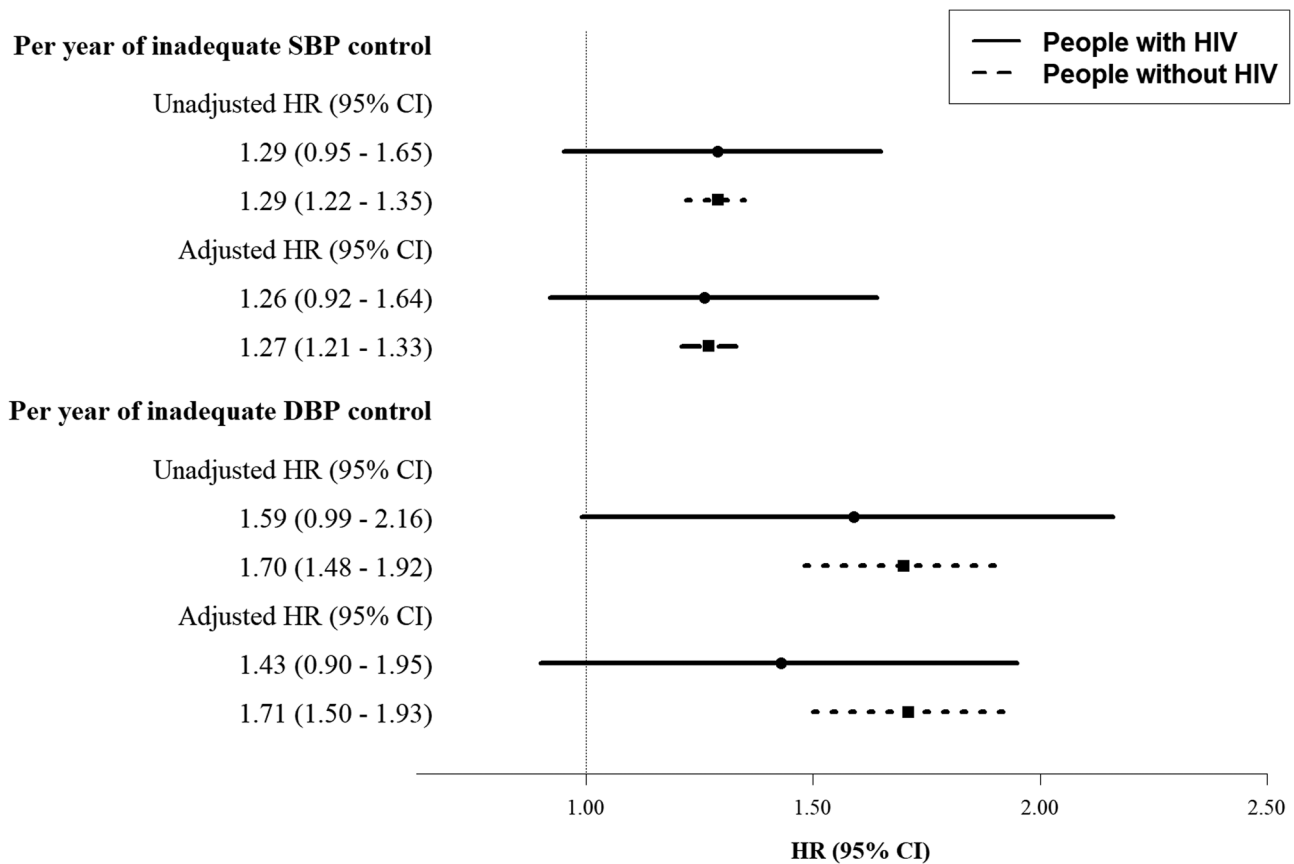


Fig. 1. Risk of incident dementia in people with and without HIV per year of inadequate hypertension control. Adjusted models accounted for baseline age, sex, race/ethnicity, neighborhood-level socioeconomic status, smoking, substance use disorders, cardiovascular disease, cerebrovascular disease, obesity, diabetes, mental health (depression or anxiety), and healthcare utilization.

A limitation to consider is that reverse causality cannot be ruled out since the pathological process of dementia can affect blood pressure regulation, and the gradual progression of dementia can span many years before clinically recognized disease. Dementia may also impact hypertension medication adherence, resulting in worse blood pressure control. These are not expected to differ substantially by HIV status and would likely have had minimal impact on our results, though analyses completed over longer follow-up periods could help better understand potential bidirectional effects of hypertension control and dementia.

Conclusion

This study suggests that, among adults with hypertension, the association of inadequate hypertension control with greater dementia risk is similar by HIV status. We found no evidence that worse hypertension control explains the greater cumulative incidence of dementia among people with HIV. Stronger associations of DBP control with dementia risk should be investigated further. Collectively, these results reinforce the importance of effective

hypertension prevention, diagnosis, and control for reducing risk of developing dementia in older age.

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J.O.L. conceptualized and designed the study, interpreted the data, and drafted the manuscript. C.E.H. and C.L. interpreted the data and provided critical input on the manuscript. Z.S.Y. conducted the data analysis, interpreted the data, and provided critical input on the manuscript. T.L. collected data, calculated the disease management index, and provided critical input on the manuscript. M.A. H. and D.D.S. interpreted the data and provided critical input on the manuscript. M.J.S. contributed to study conceptualization and design, data interpretation, and provided critical input on the manuscript.

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Conflicts of interest

The authors report no conflicts of interest.

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