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Incidence and contributing factors of dementia among people living with HIV in British Columbia, Canada, from 2002 to 2016: a retrospective cohort study

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ABSTRACT

Introduction Dementia is a progressive and debilitating disease, and people living with HIV (PLWH) often develop dementia much earlier than those not living with HIV. We estimated the incidence and prevalence of dementia and identified its key risk factors in a cohort of PLWH in British Columbia, Canada.

Methods This retrospective cohort study used data from the Seek and Treat for Optimal Prevention of HIV/AIDS study. Eligible individuals were diagnosed with HIV, ≥40 years of age, naïve to antiretroviral therapy (ART), had no dementia at the index date and were followed for ≥1 year during 2002–2016. Our main outcome was incident dementia. We examined the effect of sociodemographic and clinical covariates on the incidence of dementia using a cause-specific hazard (CSH) model, with all-cause mortality as a competing risk event.

Results Among 5121 eligible PLWH, 108 (2%) developed dementia. The crude 15-year prevalence of dementia was 2.1%, and the age–sex standardised incidence rate of dementia was 4.3 (95% CI: 4.2 to 4.4) per 1000 person-years. Among the adjusted covariates, CD4 cell count<50 cells/mm^3 (adjusted CSH (aCSH) 8.61, 95% CI: 4.75 to 15.60), uncontrolled viremia (aCSH 1.95, 95% CI: 1.20 to 3.17), 10-year increase in age (aCSH 2.41, 95% CI: 1.89 to 3.07), schizophrenia (aCSH 2.85, 95% CI: 1.69 to 4.80), traumatic brain injury (aCSH 2.43, 95% CI: 1.59 to 3.71), delirium (aCSH 2.27, 95% CI: 1.45 to 3.55), substance use disorder (SUD) (aCSH 1.94, 95% CI: 1.18 to 3.21) and mood/anxiety disorders (aCSH 1.80, 95% CI: 1.13 to 2.86) were associated with an increased hazard for dementia. Initiating ART in 2005–2010 (versus<2000) produced an aCSH of 0.51 (95% CI: 0.30 to 0.89).

Conclusions We demonstrated the negative role of immunosuppression and inflammation on the incidence of dementia among PLWH. Our study also calls for the enhanced integration of care services provided for HIV, mental health, SUD and other risk-inducing comorbidities as a means of lowering the risk of dementia within this population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ People living with HIV (PLWH) experience an excess risk and earlier onset of dementia compared with HIV-negative individuals. Considering that more PLWH are living long enough to reach older adulthood, a rise in the incidence of dementia is expected within this population.

WHAT THIS STUDY ADDS

⇒ This study estimated the incidence and prevalence of dementia among a large cohort of PLWH and identified low CD4 cell count, HIV viremia, traumatic brain injury, delirium and mental health and substance use disorders as key risk factors contributing to a higher hazard for dementia within this population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides healthcare professionals and policy-makers with a comprehensive overview of the burden of dementia among PLWH and enhances their ability to effectively design preventative measures and targeted interventions to reduce the burden of dementia in this population.

INTRODUCTION

Before the widespread use of antiretroviral therapy (ART), HIV-associated dementia (HAD), caused by the direct impacts of HIV and opportunistic infections in the brain, was highly prevalent among people living with HIV (PLWH).[1] However, with modern ART and effective HIV control, HAD has become rare.[2] While the reduction of HAD among PLWH has succeeded, this population is still at a higher risk for dementia, with the onset of non-HAD occurring 14 to 21 years earlier than among HIV-negative individuals.[2 3] Dementia is associated with high levels of disability and functional impairment, increased

rates of all-cause mortality and higher healthcare costs.[4] Therefore, the high burden of dementia among PLWH raises public health concerns.

Other types of dementia, including Alzheimer's disease, Creutzfeldt-Jakob disease, Lewy body dementia, frontotemporal dementia and mixed dementia, can manifest among PLWH, each with a different symptomology.[5 6] Although we do not fully understand the causes of each type of dementia, we know that this is a progressive disease which can be related to ageing, genetics/family history, health conditions and environmental and behavioural factors.[4–7] The most common type of dementia is Alzheimer's disease globally, and its risk increases with age.[4 6–9] In Canada, 25% of people over 85 years are diagnosed with dementia, and the risk of dementia is estimated to double every 5 years past age 65.[7] With increased life expectancy among PLWH, a rise in the incidence of dementia is expected. However, disparities in the risk of dementia among PLWH and HIV-negative individuals with comparable age show that other factors are involved.[2]

PLWH are disproportionately affected by other comorbidities that have an established association with cognitive impairment and dementia.[10] Studies of the general population have identified cardiovascular disease (CVD), hypertension, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), traumatic brain injury (TBI), delirium, mental health disorders and substance use disorder (SUD) as risk factors for dementia.[11–18] The impact of these comorbidities on the incidence of dementia may be exacerbated for PLWH, since these risk factors are significantly more prevalent in this population.[2 3 19] PLWH are also more likely to experience socioeconomic disadvantages, which are associated with dementia incidence in the general population. Such socioeconomic disadvantages include poor education, unemployment, poor housing standards and living in disadvantaged neighbourhoods.[20 21] In addition to risk-inducing comorbidities and socioeconomic factors, clinical outcomes of HIV infection and the prolonged use of ART can impact the risk of dementia. HIV-related inflammation in the brain, which can persist even with continuous use of ART and long-term viral suppression, and potential neurotoxic ART side effects are some of the clinical factors associated with neurocognitive impairments among PLWH.[10] Thus, factors unique to PLWH may contribute to the higher risk of dementia in this population.

Few studies have been conducted to characterise the risk factors of incident dementia among PLWH, and only a few factors were controlled for in their analysis.[19 22] This study aimed to estimate the incidence and prevalence of dementia and examined the contributing effect of the key risk factors using a population-level cohort of PLWH in British Columbia, Canada.

METHODS

Data source

This retrospective study used longitudinal individual-level data from the Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS) population-based cohort.[23] STOP HIV/AIDS was created through linkages between the British Columbia Centre for Excellence in HIV/AIDS Drug Treatment Program and various province-wide administrative health datasets provided by the British Columbia Ministry of Health (BC-MoH). The linked datasets contain demographic, clinical, drug treatment, laboratory and mortality data on all diagnosed PLWH in British Columbia.[24 25] Detailed descriptions of these linked datasets are provided in online supplemental table S1.

Study design

Eligible individuals in the STOP HIV/AIDS cohort had to meet the following criteria: (1) being diagnosed with HIV, (2) ART initiation between 1 January 1997 and 31 December 2015, (3) 40 years or older at the index date, (4) no dementia diagnosis before the index date, (5) having at least one viral load measured at the index date or during follow-up, (6) ART naïve and having a viral load>50 copies/mL at the index date, (7) having at least 1-year follow-up and (8) having at least one CD4 cell count at the index date or during follow-up. The index date (ie, the start of follow-up) for each individual was the latest of the following dates: 5 years since the first administrative date (ie, date of registration for British Columbia Medical Services Plan or the first record of an encounter with British Columbia's healthcare system), first viral load or ART initiation date (ie, first encounter with the healthcare system related to an HIV service), 40th birthday (ie, the dementia case-finding algorithm requires PLWH to be at least 40 years) or 1 January 2002. The 5-year window was chosen to account for differences in the availability of medical records for people who had lived in British Columbia for many years and people who recently came to the province. Also, we used this window to allow for the identification of prevalent comorbidities at the index date. Eligible individuals were followed until the earliest of the following dates: dementia diagnosis, death, loss to follow-up or 31 December 2016.

Patient and public involvement

Patients or the public were not involved in this research study's design, implementation and interpretation.

Outcome variable

Our outcomes of interest were the period prevalence (henceforth referred to as prevalence) and incidence of dementia. Cases of dementia were identified annually among individuals aged 40 years and older by the BC-MoH case-finding algorithm based on the International Classification of Disease—Ninth and Tenth Revision (ICD 9/10) diagnostic codes and drug identification numbers. Our case definition is outlined in online supplemental table S2 and includes Alzheimer's disease, vascular, Lewy body, frontotemporal dementia, HAD and dementia related to other classified diseases. Note that the BC-MoH's case-finding algorithm was modified

according to expert opinion (FV-R) to include cases of frontotemporal dementia. A lookback window of 5 years before the index date was used to identify incident cases of dementia and exclude prevalent cases.[26] The concept of a lookback window is important when working with administrative databases. Administrative databases do not collect data for research, and therefore, a person's information only shows up in the data if they use a specific service captured by one of the databases. Also, the longer a person has been engaged in the healthcare system, the more likely this person will have an incident or prevalent condition identified. Thus, to control for this bias, we need to systematically scan people's records, applying a lookback window that has the same length for all individuals. The choice for the length of the lookback window is a compromise between minimising misclassification bias and maximising sample size and study follow-up period.

We calculated the age–sex standardised annual prevalence and incidence rate of dementia using British Columbia's 2011 census as the reference population for the standardisation.[27 28] The annual prevalence was the proportion of the population present for ≥1 day in a given year who had dementia. The 15-year prevalence was the proportion of the study population diagnosed with dementia from 2002 to 2016 (overall and stratified by age and sex). The overall incidence rate of dementia was the sum of annual incident cases per 1000 person-years (PYs) at risk of developing dementia, and the corresponding 95% CI were calculated using the mid-p exact test.[20] The sex-stratified incidence rates were standardised by age, and the age-stratified incidence rates were standardised for sex. To ensure sufficient observations, we categorised age as 40–44, 45–49, 50–54, 55–59 and 60+ years.

Covariates

Sociodemographic covariates included sex at birth (male/female), age (continuous), ethnicity (white, non-white, unknown), history of housing instability (yes/no) and history of residency in the Downtown Eastside (DTES) (yes/no). DTES is a neighbourhood within the city of Vancouver known for its social and economic inequities and one of the HIV epidemic epicentres among people with a history of injecting drug (PWID) use.[29] We used the first three digits of postal codes to identify individuals with a history of residency in the DTES. The ICD 9/10 diagnostic codes for inadequate housing, lack of housing and homelessness were used to determine the history of housing instability.[30] Housing instability and residency of the DTES were assessed annually for 5 years (lookback window) before the index date.

Clinical covariates included the presence (yes/no) of comorbidities during the period spanning from 5 years (ie, lookback window) before the index date to the end of follow-up. The comorbidities included CVD, CKD, diabetes, COPD, hypertension, delirium, schizophrenia, mood/anxiety disorders, SUD and TBI. The number of TBI episodes experienced was also included as a covariate in the descriptive analysis. Comorbidities were identified by applying the appropriate BC-MoH case-finding algorithm (online supplemental table S2). The case definition used for episodes of delirium was previously validated using direct evaluation of postsurgical patients in an intensive care unit, which was reported to be sensitive to the use of alcohol and medications associated with delirium in PLWH.[31–33] Once identified, comorbidities were assumed to be irreversible and present until the end of follow-up. Other clinical covariates included viral load at index date (<200, ≥200 copies/mL), uncontrolled viremia (ie, ≥two consecutive viral loads>200 copies/mL; yes, no, not measured; assessed annually),[34] CD4 cell count (<50 cells/mm^3, 50–199 cells/mm^3, 200–349 cells/mm^3, ≥350 cells/mm^3; not measured; assessed annually), self-reported HIV acquisition risk category (PWID, gay, bisexual and other men who have sex with men (gbMSM), heterosexual/other, unknown) and ART initiation year (<2000, 2000–2004, 2005–2010 and >2010). ART initiation was chosen to represent the cohort effect, since it reflects how the population has changed over time with changes in ART treatment guidelines, availability of new ARTs, subgroups of the population initiating ART (initially the HIV epidemic was predominant among gbMSM and then PWID) and interventions put in place in British Columbia to address the HIV epidemic.[1 23] The cut-off points for the categories of ART initiation year were chosen to reflect these changes while taking into account the power needed to conduct this study.

Statistical analysis

The $\chi 2$ and Kruskal-Wallis tests compared categorical and continuous covariates, respectively.[35] Multicollinearity was assessed using the polychoric correlation technique.[36] We used the cause-specific hazard (CSH) model, a survival analysis, to identify factors associated with an increased hazard for dementia with all-cause mortality as a competing risk event.[37] The CSH model is better suited than the Fine-Gray subdistribution model to accommodate time-varying covariates and when the intent is to study the aetiology of diseases.[38 39] In this model, all-cause mortality competes with the dementia diagnosis since individuals who die are no longer at risk of dementia and are excluded from our risk set. The CSH ratio is a measure of 'aetiological association'. It measures the instantaneous rate of dementia in PLWH who have experienced neither our event of interest (dementia) nor the competing event (death).[37] Considering that all-cause mortality was also an outcome variable for those never diagnosed with dementia, we calculated age–sex standardised all-cause mortality rates for our study population. The covariates included in the model were selected through an elimination process that uses the Akaike information criterion and type III p values.[40] All statistical analyses were conducted using SAS V.9.4 and R V.4.0.2.

Sensitivity analyses

Given that dementia may affect males and females differently and there is inconclusive data about sex

differences,[41] we performed sex-stratified analyses. We conducted a time-to-event analysis for incident dementia using Kaplan-Meier (KM) curves and built separate models to assess the risk factors that may explain the incidence of dementia by sex. We also performed a stratified analysis for the history of residency in the DTES, given that the population in this geographical area is highly vulnerable and may have a higher risk of developing dementia.[29]

RESULTS

Study population

In total, 5121 participants were eligible for this study. The step-by-step inclusion process is outlined in online supplemental figure S1. In the index year, 62 PLWH had pre-existing dementia and were excluded from the study. Among those included, 108 (2%) developed dementia, 762 (15%) died during the study, 4078 (80%) were alive at the study end date and did not develop dementia and 173 (3%) were lost to follow-up. Table 1 describes the sociodemographic and clinical characteristics of the study population at the index date and end of follow-up, given that some of the variables were time-varying.

Table 2 compares the sociodemographic and clinical characteristics of PLWH with and without incident dementia. Compared with PLWH without incident dementia, those with incident dementia were older both at the index date (48 vs 43 years) and end of follow-up (55 vs 52 years). Note that for PLWH with dementia, in this study, age at the end of follow-up is equivalent to the age at dementia diagnosis (median 55, 25th to 75th percentile (Q1–Q3): 48–62 years). PLWH with dementia were also more likely to be PWID and have CD4<50 cells/mm^3 and uncontrolled viremia at the end of follow-up. Additionally, these individuals were more likely to have initiated ART in earlier years (before 2005), and all comorbidities except diabetes were significantly more common among those with dementia.

Prevalence and incidence of dementia and all-cause mortality rates

Table 3 displays the crude 15-year prevalence and standardised incidence rates of dementia and all-cause mortality rates in our overall study population, stratified by sex and age. The age–sex standardised annual estimates can be found in online supplemental table S3. The crude 15-year prevalence of dementia was 2.1%, the age–sex standardised incidence rate of dementia was 4.3 (95% CI: 4.2 to 4.4) per 1000 PYs, and the age–sex standardised all-cause mortality rate was 24.3 (95% CI: 24.1 to 24.5) per 1000 PYs in the overall study population. The 15-year prevalence of dementia was higher among males, while the age-standardised incidence rate of dementia and the age-standardised all-cause mortality rate was higher among females.

Multivariable CSH models

HIV acquisition risk group and history of residency in the DTES were excluded from our multivariable analysis

Table 1 Sociodemographic and clinical characteristics of the overall study population

Categorical variables	Overall (n=5121) N (%)
End of follow-up status	
Dementia	108 (2)
Death	762 (15)
Alive	4078 (80)
Loss to follow-up	173 (3)
Sex (at birth)	
Female	870 (17)
Male	4251 (83)
HIV acquisition risk	
PWID	1657 (32)
gbMSM	1693 (33)
Heterosexual/other	1208 (24)
Unknown	563 (11)
Ethnicity	
White	2040 (40)
Non-white	936 (18)
Unknown	2145 (42)
CD4 cell count (at the index date)	
<50 cells/mm^3	571 (11)
50–199 cells/mm^3	1526 (30)
200–349 cells/mm^3	1545 (30)
≥350 cells/mm^3	1454 (29)
Not measured	25 (0)
CD4 cell count (at the end of follow-up)	
<50 cells/mm^3	208 (4)
50–199 cells/mm^3	559 (11)
200–349 cells/mm^3	747 (14)
≥350 cells/mm^3	3005 (59)
Not measured	602 (12)
Viral load (at the index date)	
<200 copies/mL	24 (0)
≥200 copies/mL	5097 (100)
Uncontrolled viremia (at the end of follow-up)	
No	3927 (77)
Yes	495 (10)
Not measured	699 (13)
ART initiation year	
<2000	1119 (22)
2000–2004	1125 (22)
2005–2010	1841 (36)
>2010	1036 (20)
Cardiovascular disease*	
No	4488 (88)

Continued

Table 1 Continued

Categorical variables	Overall (n=5121) N (%)
Yes	633 (12)
Chronic kidney disease*	
No	4626 (90)
Yes	495 (10)
Diabetes*	
No	4595 (90)
Yes	526 (10)
Chronic obstructive pulmonary disease*	
No	4597 (90)
Yes	524 (10)
Hypertension*	
No	4218 (82)
Yes	903 (18)
Delirium*	
No	4310 (84)
Yes	811 (16)
Schizophrenia*	
No	4812 (94)
Yes	309 (6)
Mood/anxiety disorder*	
No	2515 (49)
Yes	2606 (51)
Substance use disorder*	
No	3107 (61)
Yes	2014 (39)
Traumatic brain injury*	
No	4492 (88)
Yes	629 (12)
History of housing instability	
No	4852 (95)
Yes	269 (5)
History of residency in the DTES	
No	4384 (86)
Yes	737 (14)
Continuous variables	Median (Q1–Q3)
Age (at the index date)	44 (40–50)
Age (at the end of follow-up)	52 (47–58)
Total follow-up time (years)	7.18 (4.07–11.12)
Traumatic brain injury episodes (n)†	1 (1–2)

*Diagnosed during the period spanning from 5 years prior to the index date to the end of follow-up.
†Excluded zeros for the median, Q1 and Q3.
DTES, Downtown Eastside; gbMSM, gay, bisexual and other men who have sex with men; PWID, people with a history of injecting drugs; Q1–Q3, 25th to 75th percentile.

due to multicollinearity with SUD and history of unstable housing. With over 40% missing information, ethnicity was also excluded. Figure 1 illustrates the adjusted CSH (aCSH) ratios for dementia. Among all the adjusted covariates, CD4 cell count<50 cells/mm^3, relative to ≥350 cells/mm^3, had the strongest association with dementia (aCSH 8.61, 95% CI: 4.75 to 15.60). Uncontrolled viremia (aCSH 1.95, 95% CI: 1.20 to 3.17) was also associated with an increased aCSH for dementia. Every 10-year increase in age increased the aCSH for dementia by more than twofold (aCSH 2.41, 95% CI: 1.89 to 3.07). Among the comorbidities, schizophrenia (aCSH 2.85, 95% CI: 1.69 to 4.80), TBI (aCSH 2.43, 95% CI: 1.59 to 3.71) and delirium (aCSH 2.27, 95% CI: 1.45 to 3.55) had the strongest association with dementia. Although the associations of SUD (aCSH 1.94, 95% CI: 1.18 to 3.21) and mood/anxiety disorders (aCSH 1.80, 95% CI: 1.13 to 2.86) were more modest, they also increased the aCSH for dementia. The only factor associated with a reduced aCSH for dementia was ART initiation year between 2005 and 2010 (aCSH 0.51, 95% CI: 0.30 to 0.89). Thus, it shows that the aCSH for the incidence of dementia was 49% lower for those who initiated ART between 2005 and 2010, compared with those who initiated before the year 2000.

The aCSH ratios for mortality are presented in figure 2. CD4 cell count<350 cells/mm^3 and uncontrolled viremia had statistically significant associations with increased aCSH for death. Among the comorbidities, CVD, CKD, COPD, SUD and delirium were associated with an increased aCSH for death. Mood/anxiety disorders and ART initiation after 2010 were the only factors associated with a reduced aCSH for death.

Sensitivity analysis

The covariate distribution of the study population stratified by sex is provided in online supplemental table S4. Compared with males, females were significantly more likely to have all comorbidities except CVD and diabetes, history of unstable housing, injection drug use and residency in the DTES and<200 cells/mm^3 CD4 counts at the end of follow-up. We conducted a time-to-event analysis for dementia using KM curves. We found no statistically significant difference between time-to-dementia diagnosis among males and females (online supplemental figure S2). We did not see a statistically significant difference between males and females regarding the incidence of dementia. The aCSH ratios of dementia for females and males are presented in online supplemental figures S3 and S4, respectively. The aCSH ratios of death for females and males are presented in online supplemental figures S5 and S6, respectively. Factors associated with dementia among our male population were the same as in our overall model. Although the CIs for the aCSH ratios of dementia in the female-stratified model were wide, we observed that for females, only age, having a CD4 cell count<50 cells/mm^3, CVD and schizophrenia were significantly associated with dementia.

Table 2 Sociodemographic and clinical characteristics of people living with HIV in British Columbia, Canada, from 2002 to 2016, stratified by incident dementia

	PLWH with incident dementia, n=108	PLWH without incident dementia, n=5013	
Categorical covariates	**N (row %)**	**N (row %)**	**P values**
Sex (at birth)			
Female	14 (2)	856 (98)	0.2601
Male	94 (2)	4157 (98)	
HIV acquisition risk			
PWID	53 (3)	1604 (97)	0.0002
gbMSM	19 (1)	1674 (99)	
Heterosexual/other	29 (2)	1179 (98)	
Unknown	7 (1)	556 (99)	
Ethnicity			
White	49 (2)	1991 (98)	0.3137
Non-white	17 (2)	919 (98)	
Unknown	42 (2)	2103 (98)	
CD4 cell count (at the index date)			
<50 cells/mm^3	22 (4)	549 (96)	0.0031
50–199 cells/mm^3	35 (2)	1491 (98)	
200–349 cells/mm^3	20 (1)	1525 (99)	
≥350 cells/mm^3	27–30 (2–2)*	1424–1427 (98–98)*	
Not measured	<5†	21–24 (84–96)*	
CD4 cell count (at the end of follow-up)			
<50 cells/ mm^3	26 (12)	182 (88)	<0.0001
50–199 cells/mm^3	17 (3)	542 (97)	
200–349 cells/mm^3	22 (3)	725 (97)	
≥350 cells/mm^3	31 (1)	2974 (99)	
Not measured	12 (2)	590 (98)	
Viral load (at the index date)			
<200 copies/mL	0 (0)	24 (100)	0.4711
≥200 copies/mL	108 (2)	4989 (98)	
Uncontrolled viremia (at the end of follow-up)			
No	62 (2)	3865 (98)	<0.0001
Yes	35 (7)	460 (93)	
Not measured	11 (2)	688 (98)	
ART initiation year			
<2000	41 (4)	1078 (96)	<0.0001
2000–2004	40 (4)	1085 (96)	
2005–2010	22 (1)	1819 (99)	
>2010	5 (0)	1031 (100)	
Cardiovascular disease‡			
No	83 (2)	4405 (98)	0.0006
Yes	25 (4)	608 (96)	
Chronic kidney disease‡			
No	89 (2)	4537 (98)	0.0048
Yes	19 (4)	476 (96)	

Continued

Table 2 Continued

Categorical covariates	PLWH with incident dementia, n=108 N (row %)	PLWH without incident dementia, n=5013 N (row %)	P values
Diabetes‡			
No	93 (2)	4502 (98)	0.2107
Yes	15 (3)	511 (97)	
Chronic obstructive pulmonary disease‡			
No	89 (2)	4508 (98)	0.0107
Yes	19 (4)	505 (96)	
Hypertension‡			
No	80 (2)	4138 (98)	0.0223
Yes	28 (3)	875 (97)	
Delirium‡			
No	66 (2)	4244 (98)	<0.0001
Yes	42 (5)	769 (95)	
Schizophrenia‡			
No	88 (2)	4724 (98)	<0.0001
Yes	20 (6)	289 (94)	
Mood/anxiety disorder‡			
No	27 (1)	2488 (99)	<0.0001
Yes	81 (3)	2525 (97)	
Substance use disorder‡			
No	36 (1)	3071 (99)	<0.0001
Yes	72 (4)	1942 (96)	
Traumatic brain injury‡			
No	72 (2)	4420 (98)	<0.0001
Yes	36 (6)	593 (94)	
History of unstable housing			
No	98 (2)	4754 (98)	0.0593
Yes	10 (4)	259 (96)	
History of residency in the DTES			
No	94 (2)	4290 (98)	0.6690
Yes	14 (2)	723 (98)	
Continuous covariates	Median (Q1–Q3)	Median (Q1–Q3)	
Age (at the index date)	48 (42–56)	43 (40–50)	<0.0001
Age (at the end of follow-up)	55 (48–62)	52 (47–58)	0.0123
Total follow-up time	5.78 (3.72–8.30)	7.23 (4.07–11.16)	0.0004
Traumatic brain injury episodes (n)§	1 (1–2.5)	1 (1–2)	0.7849

P value estimates exclude 'unknown' categories; p value significance is set at 0.05. For PLWH with dementia, the end of follow-up is marked by the date of dementia diagnosis, and for PLWH without dementia, the end of follow-up is either the date of death, the end of the study or the date of loss to follow-up.
*Due to privacy concerns, small cell counts (<5) were protected by displaying a number range.
†Due to data privacy, we replaced exact numbers if cells contained <5 participants.
‡Diagnosed during the period spanning from 5 years prior to the index date to the end of follow-up.
§Excluded zeros for the median, Q1 and Q3.
DTES, Downtown Eastside; gbMSM, gay, bisexual and other men who have sex with men; PWID, people with a history of injecting drugs; Q1–Q3, 25th to 75th percentile.

Table 3 15-year prevalence and standardised incidence rates of dementia and mortality rates in our study population from 2002 to 2016

	15-year prevalence of dementia (%)	Incidence rate of dementia (per 1000 PYs) (95% CI)	Mortality rate (per 1000 PYs) (95% CI)
Overall	2.1	4.3 (4.2 to 4.4)	24.3 (24.1 to 24.5)
Sex			
Female	1.6	4.7 (4.6 to 4.8)	27.2 (27.0 to 27.4)
Male	2.2	3.8 (3.7 to 3.9)	21.3 (21.1 to 21.5)
Age (years)			
40–44	2.2	1.3 (1.2 to 1.3)	14.8 (14.7 to 15.0)
45–49	1.4	1.4 (1.3 to 1.4)	25.3 (25.1 to 25.5)
50–54	1.6	2.8 (2.8 to 2.9)	23.8 (23.6 to 24.0)
55–59	2.2	3.2 (3.1 to 3.2)	26.6 (26.4 to 26.8)
60+	3.2	7.2 (7.1 to 7.3)	26.6 (26.4 to 26.8)

Prevalence estimates are unadjusted. The overall incidence rate of dementia and mortality rate were standardised for age and sex, sex-stratified incidence rates were standardised for age, and age-stratified incidence rates were standardised for sex.
PYs, person-years.

The stratified analysis by the history of residency in the DTES is displayed in online supplemental table S5. Compared with PLWH without a history of residency in the DTES, those with a history of living in the DTES were younger at the index date (43 vs 44) and had longer follow-up time (7.84 vs 7.08). They were significantly more likely to have SUD, TBI and all other comorbidities except hypertension. Moreover, they were significantly more likely to have <200 cells/mm^3 CD4 counts at the end of follow-up, unsuppressed viral loads both at the index date and the end of follow-up and a greater number of TBI episodes.

We also built stratified models for PLWH with and without a history of residency in the DTES to separately assess the risk factors associated with dementia within these populations and mitigate the possibility of selection bias. The aCSH ratios of dementia among PLWH with and without a history of residency in the DTES are presented in online supplemental figures S7 and S8, respectively. The aCSH ratios of death among PLWH with and without a history of residency in the DTES are presented in online supplemental figures S9 and S10, respectively. All factors associated with incident dementia among PLWH without a history of residency in the DTES were the same as the overall model, except for CVD. Among PLWH without a history of residency in the DTES, CVD was significantly associated with dementia. Among PLWH with a history of residency in the DTES, only age, diabetes, schizophrenia and TBI were significantly associated with incident dementia. Note that the CIs for the aCSH ratios of dementia in this model were wide.

DISCUSSION

In this study, we estimated the prevalence and incidence rate of dementia and identified several clinical risk factors associated with the incidence among a large cohort of ART-treated PLWH with a long (15 years) observation period. Previous studies of dementia have mainly focused on older adults in the general population,[8] but our study was conducted among a younger population and those living with HIV. Our estimated prevalence and incidence rate of dementia among PLWH in British Columbia was higher than that of the general older adult populations in high-income countries.[8] Note that in British Columbia, the age-standardised dementia incidence rate in the general population has been stable since the year 2000, at around 0.5%, which is four times lower than what we estimated to be among PLWH (ie, 2%).[42] Therefore, our findings address a knowledge gap in the epidemiology of dementia among PLWH.

Congruent with previous studies, we found that advanced immunosuppression and inflammation were some of the main drivers of the incidence of dementia, especially in this young population.[10 43 44] Initiating ART in earlier years was also associated with an increased hazard for dementia. The fact that PLWH who recently enrolled in the ART programme had a lower hazard of developing dementia can be explained by contemporary HIV treatment guidelines, which recommend starting ART as early as possible to prevent the extensive deterioration of the immune system. Moreover, the use of less toxic antiretrovirals in recent years could have also contributed to a lower likelihood of developing dementia. In our study, we considered uncontrolled viremia a proxy variable for inflammation in PLWH. In studies of the general population, inflammation has been linked to cognitive decline and an increased risk of developing dementia.[43 44] While we believe that immunosuppression and inflammation concurrently contribute to the risk of dementia, we acknowledge that understanding the pathophysiology of cognitive impairment and dementia with respect to these risk factors requires further investigations, especially

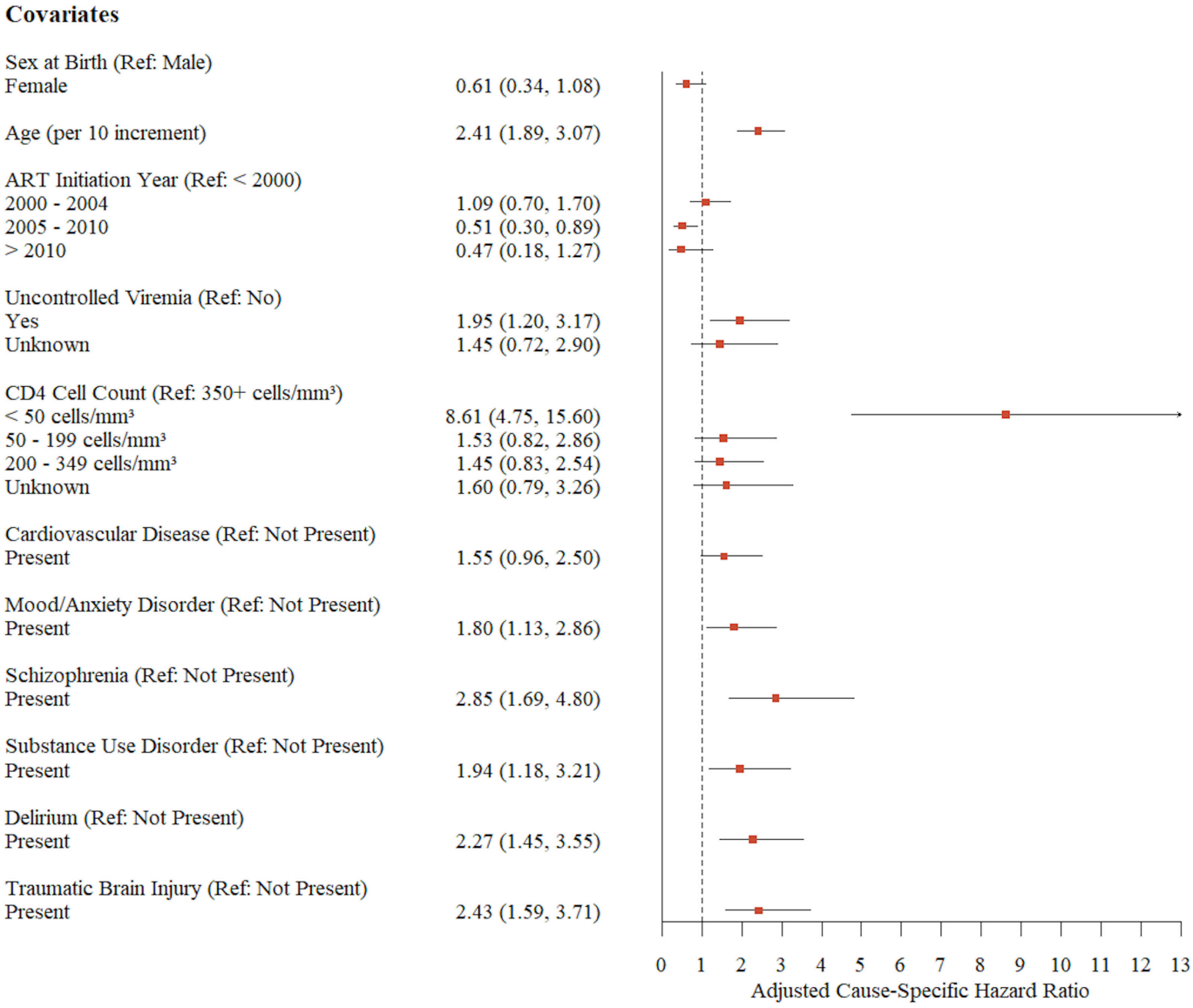

Figure 1 Forest plot presenting the adjusted cause-specific hazard ratios for dementia. Variables not selected included diabetes, hypertension, mood/anxiety disorder and history of housing instability. ART, antiretroviral therapy.

among PLWH. Second, our findings can be explained by factors such as incomplete ART adherence and inadequate retention in HIV care, which often lead to uncontrolled viremia and immunosuppression. Last, people living with dementia experience progressive cognitive decline and age-associated changes that may affect their ability to self-manage their disease. Consequently, these individuals are at a higher risk of missing medical appointments, not filling/refilling prescriptions and forgetting to take their medications.[45–47] Among PLWH, this issue is magnified since this highly vulnerable population has a high prevalence of mental health conditions, SUD, TBI and structural barriers (eg, housing instability). Thus, interventions such as SMS/text messages, telehealth/telemedicine, peer and social support, improved access to support services (eg, treatment/counselling for mental health, SUD) and cash incentives to help individuals with transportation, housing, childcare and financial needs are some of the interventions that have been shown to be effective in individuals living with both HIV and dementia.[45–52]

We also found schizophrenia, mood/anxiety disorders, SUD and delirium to be associated with an increased hazard for dementia, with schizophrenia having the strongest association among all the comorbidities assessed. These associations may have been partially attributed to other risk factors, such as the use of antipsychotic medication and lifestyle behaviours, including alcohol use, smoking and physical inactivity among those with these comorbidities.[16–18] In particular, the association between schizophrenia, formerly called the dementia praecox (premature dementia), and incident dementia may also be due to the synergic effects of the neurobiological and pathophysiological characteristics of schizophrenia that are risk factors for dementia.[53] While the association between SUD and dementia is evident in the literature,[18]

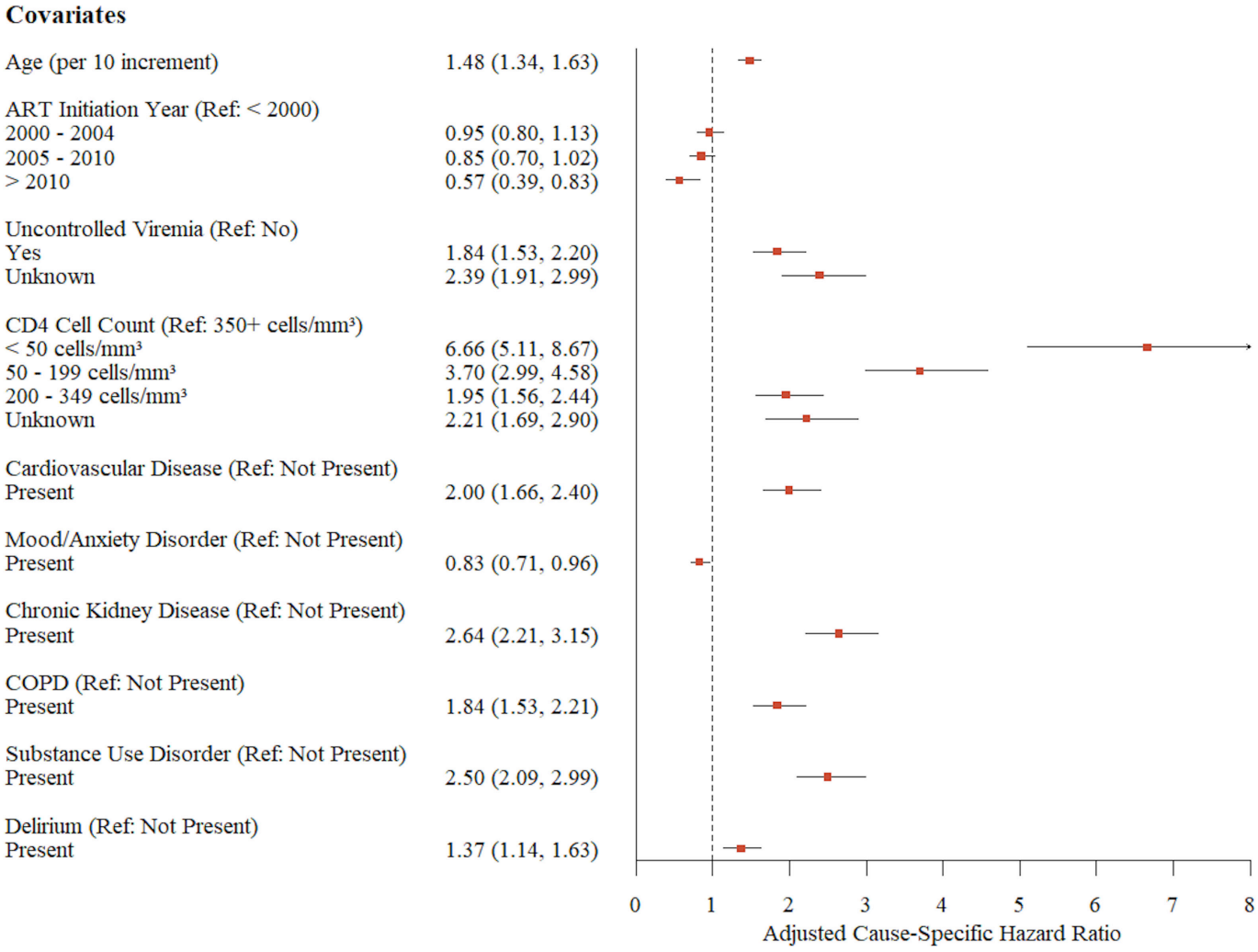

Figure 2 Forest plot presenting the adjusted cause-specific hazard ratios for death. Note: variables not selected included sex at birth, diabetes, hypertension, schizophrenia, traumatic brain injury and history of housing instability. ART, antiretroviral therapy.

the strength of this association may depend on the types of substances and severity of use.[54 55] Episodes of delirium are increasingly recognised as risk factors for dementia, although they may be part of a pathway from alcohol use to a greater risk for dementia.[16 33] The observed higher risk of dementia among PLWH who have mental health disorders (especially schizophrenia), SUD and delirium in our population further highlights the benefits of effective treatment of mental health disorders and SUD in preventing dementia among PLWH.

Similar to studies that have focused on the general population,[15] TBI was associated with an increased hazard for dementia. Although the association between TBI and dementia has not been thoroughly studied among PLWH, evidence supports that TBI is associated with brain inflammation and neurocognitive impairment within this population.[56] Moreover, a substantial proportion of our study population had a history of residency in the DTES, where over 50% of residents were reported to have experienced at least one TBI event per year.[57] Our results also confirm that this subgroup of PLWH is significantly more likely to have TBI and experience a more significant number of TBI episodes. Previous studies have also identified a substantially higher risk of TBI in similar marginalised settings with higher rates of homelessness, substance use and crime.[58] Notably, SUD is known to have strong associations and synergic interactions with TBI that can further increase the risk of dementia.[59] TBI among marginalised individuals frequently results from falls, physical assaults and hitting one's head on objects, often in the presence of substance intoxication.[57] Since TBI is associated with dementia and other adverse health outcomes, targeted interventions such as enhancement of neighbourhood safety and effective SUD treatment are required to prevent TBIs among PLWH, especially those in marginalised neighbourhoods. Moreover, understanding the clinical and epidemiological features of dementia in relation to TBI and SUD is critical in designing preventative measures to reduce the individual and societal impacts of these conditions in our population.

Previous studies have concluded that CVD and diabetes are associated with the incidence of dementia due to lifestyle and clinical risk factors.[2 11 12 19] In our overall study population, CVD and diabetes were not associated with incident dementia after adjusting for other risk factors. A recent study suggests that having more than one cardiometabolic disease (ie, comorbidities) has a more profound association with incident dementia than the presence of these diseases individually.[60] The lack of association in our results may also be due to the effective management of these diseases, since uncontrolled diabetes is associated with a higher risk of dementia than controlled diabetes.[61] However, we could not incorporate this information since we do not have information on the control status of these conditions. Moreover, the diagnosis of dementia among PLWH may occur at an earlier age than the diagnosis of other age-associated comorbidities, such as CVD and diabetes.[3] Thus, given that the diagnosis of dementia marks the end of follow-up for individuals with incident dementia in this study, many cases of CVD and diabetes may not have been captured, resulting in a lower prevalence of CVD and diabetes in our overall study population. Interestingly, although CVD was not associated with dementia in our overall study population, it was associated with a higher risk of dementia among females. This finding aligns with the literature suggesting that females with CVD are at a higher risk for dementia than males.[62] However, survivorship bias may have also affected our results. Previous studies suggest that CVD-related mortality occurs earlier among males than females.[63] Therefore, it is plausible that death precedes dementia among males with CVD. Although our estimated age-standardised incidence rate of dementia was higher for females than males, as seen in other studies,[4 64] the 15-year prevalence of dementia was lower among females, perhaps due to their higher mortality rate. However, once we adjusted for covariates in our multivariable analysis, we did not find a significant effect of sex at birth on the hazard of dementia in our population, as shown in previous studies,[41 65] probably due to selection bias. Notably, our female population differs from other studies since a higher proportion of our female population had a history of residency in the DTES and comorbidities such as SUD, schizophrenia, mood/anxiety, delirium and TBI, which are known risk factors for dementia and all-cause mortality. Inconsistency between our results and previous findings may also be due to the fact that we considered several types of dementia, whereas other studies focused only on Alzheimer's disease. To assess if our results were influenced by bias, we conducted a sex-stratified analysis and observed that factors associated with dementia among females differed from males. Thus, our results indicate that sex-specific interventions are needed to address the heightened risk of dementia among females living with HIV.

Limitations

This study has some limitations that must be considered. First, administrative health record datasets were not collected for research purposes and may be prone to coding errors and misclassifications that may be a source of bias. The overlap of symptoms between some mental health comorbidities may have also resulted in disease misclassification. Moreover, our analysis considered SUD an irreversible diagnosis since administrative data do not identify SUD recovery accurately. We were also unable to examine the effect of specific substances and their severity on the risk of dementia. Second, we did not specifically assess the risk of dementia associated with stroke, since we complied with the BC-MOH's case-finding algorithm that subsumes stroke under CVD. Third, ethnic disparities were not accounted for since a high proportion of PLWH had unknown ethnicity. Fourth, the sample size for our female PLWH and those with a history of residency of the DTES in the stratified models was limited, and therefore, the 95% CIs for the aCSH ratios of dementia were wide. Thus, caution is warranted in interpreting these findings. Fifth, we could not control for lifestyle and socioeconomic factors such as smoking, physical activity, education, employment and income levels. We tried to compensate by including comorbidities and housing instability variables that may be proxies for these lifestyle and socioeconomic variables. Sixth, we were unable to differentiate results for HAD and non-HAD. While HAD has a unique ICD 10 diagnostic code, it does not have a specific ICD 9 code. Since the Medical Service Plan billing dataset only contains ICD 9 codes, excluding HAD was not possible. Last, the diagnosis of dementia is sometimes imprecise. It is true that some of the symptomology of dementia and some conditions (eg, delirium, depression, the effects of TBI or other causes of cognitive impairment) may present very similarly, and individuals can be erroneously diagnosed. However, in our administrative database as in electronic medical records, we rely on physicians to provide the codes for the disease that they think an individual has. Thus, this is a limitation affecting studies similar to ours.

CONCLUSION

This study provides valuable insights into the epidemiology and contributing factors of dementia among PLWH. Compared with the general population, PLWH, especially females, have a higher incidence of dementia. Given that PLWH with dementia are likely to be marginalised and disproportionately affected by mental health disorders and SUD, dementia within this ageing population will likely increase the burden on the healthcare system and lead to increased healthcare costs. Therefore, effective strategies are needed to address the risk factors of dementia among PLWH. In addition to age, we identified several clinical, HIV-specific and health-related modifiable risk factors associated with dementia. This study highlights the importance of early ART initiation,

higher CD4 cell count and controlled viremia concerning the risk of dementia among PLWH, and it emphasises the need for enhanced integration of care services provided for HIV, mental health, SUD and other risk-inducing comorbidities as a means of lowering the risk of dementia within this population.

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