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Age-standardized comparison of coronary artery disease, stroke incidence, and all-cause mortality between people living with HIV and the general population in Spain

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ABSTRACT

Objectives: We compared 15-year incidence of coronary artery disease (CAD), stroke, and all-cause mortality between people living with HIV (PLWH) and the Spanish general population.
Methods: We compared two Spanish cohorts—VACH (PLWH) and REGICOR (general population). We followed adults aged 25-74 years, free of CAD or stroke, for a mean of 15 years. We used age-standardized 15-year incidence of CAD, stroke, and all-cause mortality and compared cohorts with log-rank tests and Cox models adjusted for confounders.
Results: We included 6829 PLWH and 10,218 general population. In men aged 25-54 years with HIV, the adjusted standardized incidence rates of CAD and stroke were similar to those in the general population. In addition, PLWH had significantly higher crude all-cause standardized mortality rates than the general population: men 2790 (2536-3044) vs 1104 (1015-1192) and women 2011 (1632-2391) vs 588 (528-648) (all *P*-values <0.001). Moreover, the adjusted hazard ratio of all-cause mortality was much higher in PLWH younger than 55 years (hazard ratio 3.08 [2.42-3.90] in men and 4.71 [3.13-7.09] in women).
Conclusions: The adjusted risk of CAD and stroke among PLWH is similar to that of the general population. However, PLWH younger than 55 years still face a more than three-fold higher risk of death from any cause.
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Introduction

The introduction of antiretroviral therapy (ART) completely transformed the prognosis of HIV infection by limiting the progression of the disease. It clearly reduced the occurrence of AIDS-related complications, such as opportunistic infections and AIDS-associated malignancies [1]. Nevertheless, there is still a gap in life expectancy between people living with HIV (PLWH) and the general population with similar demographic characteristics [2]. This disparity is, in part, due to a higher prevalence of comorbidities among PLWH. PLWH are more likely to suffer from non-AIDS age-related diseases such as coronary artery disease (CAD) and stroke, diabetes, hypertension, and chronic kidney disease [3–5].

Most post-ART studies indicate that PLWH have a higher incidence of CAD and stroke than the general population with sim-

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ilar characteristics [3,6–8]. This was largely attributed to a combination of factors, including the prevalence of traditional cardiovascular risk factors, particularly smoking [5,9,10], chronic inflammation and immune activation [4,11], and dyslipidemia associated with HIV infection itself, which historically worsened with first ART regimens and did not normalize with treatment [12,13]. In addition, compared with the general population, PLWH tend to have a higher proportion of non-calcified atherosclerotic plaques, which are more prone to rupture [14,15]. On the other hand, recent studies have revealed a decrease in the incidence of CAD in PLWH during the last decades [16]. This reduction could be attributed to improved access to health care, cardiovascular risk factor control, and the use of ARTs with lower side effects on the lipid profile [4,17,18].

Although there is information on CAD and stroke incidence in PLWH, specifically in men, few studies have examined the distribution of CAD and stroke incidence and all-cause mortality by gender among PLWH [19]. Analyzing gender differences is particularly important in PLWH because their gender and age distributions often differ from the general population. In addition, comparison of age-standardized CAD, stroke incidence, and all-cause mortality between PLWH and the general population is rarely undertaken.

The aim of our study was to compare the standardized incidence rates of CAD, stroke, and all-cause mortality between men and women living with HIV and the general population.

Methods

Study design and participants

We used data from two prospective cohort studies. The VIH and AdvanCedHIV (VACH) registry of PLWH consecutively treated since 1997 at 23 Spanish HIV outpatient clinics. By 2022, the registry included baseline data for approximately 30,000 participants. For this analysis, only seven of the 24 VACH clinics were included because they provided complete longitudinal follow-up and linkage with mortality registries [9,20]. The Girona Heart Registry (REGICOR) included 11,631 participants representative of the general population from Girona province (north-eastern Spain) during the period 1995-2018 [21]. Participants in REGICOR were recruited as a representative random sample of the Girona province population, using census-based methods, and were free of CAD at baseline.

Our study included participants from both cohorts who were 25-74 years at the beginning of the study to ensure comparability with REGICOR and to reduce variability at extreme ages where numbers were small, had follow-up data available, and had no prior history of CAD and stroke at baseline.

Data collection and measurements

The VACH and REGICOR cohorts underwent a baseline examination and an interview at study inclusion. Sociodemographic information, smoking status, and prior history of high blood pressure, dyslipidemia, and diabetes were gathered using the standardized World Health Organization questionnaires [22]. In addition, anthropometric measurements, blood pressure, lipid profile, and glycaemia were assessed. Weight and height were measured, and body mass index was calculated as weight divided by squared height (kg/m^2). Systolic and diastolic blood pressure were obtained with an automatic sphygmomanometer in seated individuals after a 10-minute rest. Two readings were recorded, and the lowest value was used. Hypertension was defined as having a prior diagnosis or treatment, or systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg.

In the REGICOR cohort, enzymatic methods were used to determine the levels of total cholesterol, high-density lipoprotein cholesterol (HDL-c), triglycerides, and glucose in accredited laboratories as part of standardized clinical protocols at recruitment. Diabetes was defined as having a previous diagnosis, treatment, or a glucose level higher than 125 mg/dl. In the VACH cohort, these data were obtained from hospital laboratories' records. We also calculated the risk of CAD with the Framingham-REGICOR function, which takes into account age, sex, systolic and diastolic blood pressure, HDL-c, total cholesterol, diabetes, and smoking status [23].

Follow-up and endpoints

Follow-up was defined from study entry until the first event (CAD, stroke, or death) or censoring at last contact. Both study populations were followed up for an average of 15 years to track fatal and non-fatal first occurrence of CAD (International Classification of Diseases [ICD]-9 codes: 410-414 and ICD-10 codes: I20-I25, including subtypes) and stroke (ICD-9 codes: 430-437 and ICD-10 codes: I60-I69, including subtypes). To identify the cause of death of fatal events, both cohorts were linked with the Spanish Mortality Registry. In the REGICOR registry, non-fatal CAD and stroke incidence were identified through linkage with the REGICOR acute myocardial infarction (AMI) Registry [24] and the Program of Analytical Data for Research and Innovation in Health (PADRIS) of the Government of Catalonia. PADRIS includes all hospital admissions and the official mortality register, among other data sources. In the VACH cohort, medical records were examined for non-fatal AMI, angina, or stroke during the follow-up period. Follow-up events were recorded prospectively in medical records and retrospectively consulted for this analysis. Cases were classified based on symptoms, electrocardiogram results, and myocardial necrosis markers. If fatal AMI was only detected through the death certificate, the results of the autopsy (if available) and any related medical records were also reviewed.

Sample size

With a sample size of 6764 patients in the exposed cohort (VACH) and 10,822 participants in the unexposed cohort (REGICOR), an event rate of 1% at 10 years in the unexposed population, it is possible to detect a hazard ratio (HR) of at least 1.5 with a power exceeding 84% in a two-sided test, for a statistical significance of 5%.

Statistical analyses

Categorical variables were described as percentages and compared using the chi-squared test. Continuous variables were summarized with the mean and SD and contrasted with the Student's *t*-test, if they followed a normal distribution. Otherwise, continuous variables were described with the median and interquartile range and compared with the Mann-Whitney's U test.

Fifteen-year CAD and stroke incidence and mortality rates were standardized (direct method) by age using the European population standards [25]. Incidence of cardiovascular events was registered with the date of the first cardiovascular event. We also computed Kaplan-Meier survival curves and compared them with the log-rank statistics.

To analyze 15-year risk of cardiovascular disease and mortality in the VACH and REGICOR cohorts, we used Cox proportional hazards models, which fulfilled the proportional hazards assumption. We calculated the HR and their 95% confidence intervals. Models were adjusted for potential confounders (age, gender, blood pressure, total and HDL-c, triglycerides, diabetes, and smoking). These models were also analyzed with non-cardiovascular death as a competing risk. Finally, we tested the interaction with age and gen-

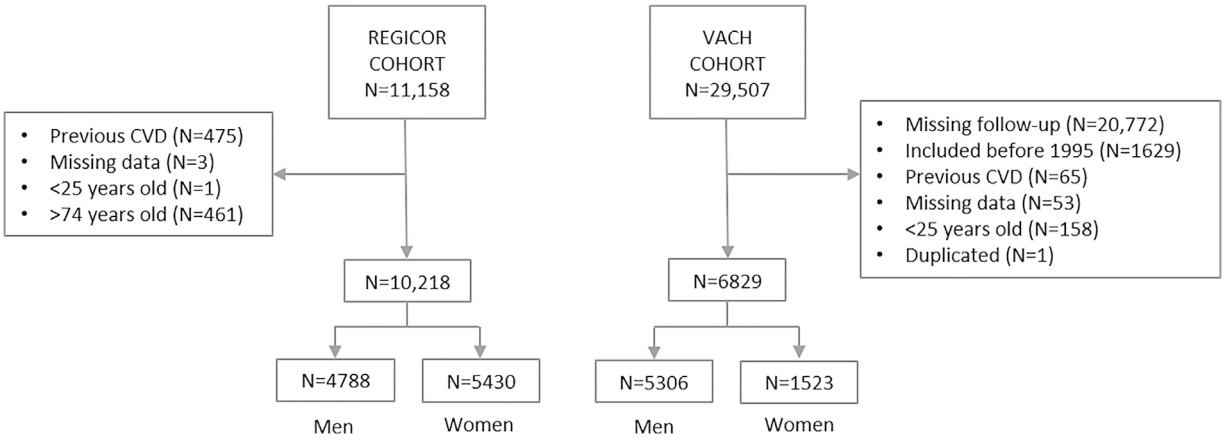


Figure 1. Flow chart of the general population cohort (REGICOR) and the people living with HIV cohort (VACH). CVD, cardiovascular disease.

der of the models. All the analyses were stratified by gender and age groups (25-54 years and 55-74 years).

Statistical significance was assumed when *P*-values were <0.05. All analyses were performed with the R software version 4.2.1 [26].

Ethical issues

All participants were duly informed and signed their consent to participate in the REGICOR and the VACH cohorts. The present study was approved by the Parc de Salut Mar Drug Research Ethics Committee (Authorization CEIm PSMAR 2018/8347-I).

Results

After the exclusion criteria, we retained 10,218 participants from the general population REGICOR cohort and 6829 from the VACH cohort (Figure 1). Median follow-up was 14.8 (10.2-15.0) years in VACH men and 13.3 (8.7-15.0) years in REGICOR men; 15.0 (12.0-15.0) years in VACH women and 13.6 (10.0-15.0) years in REGICOR women. The included PLWH had clinically significant higher diabetes, hypertension, and smoking prevalence than excluded patients (Table S1).

Table 1 presents demographic and comorbidity participant characteristics by gender, comparing the general population with PLWH. The proportion of women in the REGICOR cohort was more than twice that of the VACH. The general population participants were approximately 10 years older than PLWH. Women and men living with HIV had significantly higher levels of triglycerides and a higher prevalence of smoking. Conversely, they had lower levels of HDL-c, low-density lipoprotein cholesterol, total cholesterol, blood pressure, glucose, and body mass index. Among PLWH, the proportion of individuals with dyslipidemia, hypertension, or diabetes who were receiving treatment for these conditions was lower than in the general population, particularly among women. The prevalence of treated hypertension was 2.6-fold lower, and that of treated diabetes was 3.9-fold lower in men with HIV than in men from the general population. Women living with HIV had a 4.5 to 5.5-fold lower prevalence.

The crude standardized incidence rates are presented by gender and age groups in Table 2. Only in men aged 25-54 years, the incidence of CAD and stroke was significantly higher in PLWH than in the general population. In addition, all-cause mortality was significantly higher among men living with HIV in the two age groups and in women living with HIV aged 25-54 years. Women aged 55-74 years were too few to allow a reliable comparison of CAD or stroke incidence and all-cause mortality.

The increased age-adjusted risk of CAD and stroke was statistically significant for men living with HIV younger than 55 years. The fully adjusted models yielded no other significant HR. These comparisons remained non-significant even when fitting competing risk models.

All age and gender PLWH subgroups showed a significantly higher all-cause mortality rate compared with the general population in the Kaplan-Meier curves (Figure S1). Men living with HIV aged 25-54 years had more than three times as risk as their general population counterparts and women more than four times (Table 3). The distribution of causes of death is summarized in Table S2. Among PLWH, non-cardiovascular diseases predominated, particularly infections and liver disease, whereas cardiovascular deaths and cancer were more frequent in the general population.

Discussion

In this study, we compared the incidence of CAD, stroke, and all-cause mortality in a Spanish PLWH and general population cohorts, followed up for 15 years, and found that only men with HIV aged 25-54 years had significantly higher standardized incidence rates of CAD and stroke than the general population of the same age. In contrast, all-cause mortality standardized rates were consistently and significantly higher among PLWH, in all age and gender groups. After adjusting for relevant cardiovascular risk factors, we found no significant differences in the risk of CAD and stroke incidence between the two populations. In contrast, all-cause mortality in people younger than 55 was more than three-fold higher in PLWH than in the general population.

PLWH were at least 10 years younger than our general population reference, which contrasts with their much higher all-cause mortality. We also observed similar levels of blood pressure and HDL-c and prevalence of diabetes in the two cohorts, consistent with previous research [27,28]. As previously found in many high-income countries, the number of women was relatively small in PLWH compared with the general population distribution [29]. We observed an increased prevalence of smoking in PLWH, whose adverse effect is illustrated by the higher risk of smoking-related health complications in PLWH, encompassing all-cause mortality, cardiovascular disease, non-AIDS cancers, and bacterial pneumonia [30,31]. The high levels of triglycerides observed in PLWH also concurs with previous findings [28,32]. This increase in triglyceride levels can primarily may be partly attributed to ART, particularly when combined with protease inhibitors, nucleoside reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors [4]; however, as detailed information on ART regimens and

Table 1
Prevalence of cardiovascular risk factors in men and women from the general population and in people living with HIV.

	Men			Women		
	General population N = 4788	PLWH N = 5306	*P*-value	General population N = 5430	PLWH N = 1523	*P*-value
Age, years	52 (13)	42 (8)	<0.001	52 (12)	40 (8)	<0.001
Age group:			<0.001			<0.001
25-34	357 (7.46%)	894 (16.8%)		406 (7.48%)	377 (24.8%)	
35-44	1089 (22.7%)	2892 (54.5%)		1218 (22.4%)	791 (51.9%)	
45-54	1197 (25.0%)	1063 (20.0%)		1413 (26.0%)	256 (16.8%)	
55-64	1139 (23.8%)	357 (6.73%)		1295 (23.8%)	75 (4.92%)	
65-74	1006 (21.0%)	100 (1.88%)		1098 (20.2%)	24 (1.58%)	
Systolic blood pressure, mmHg	132 (18)	125 (17)	<0.001	124 (21)	120 (17)	<0.001
Diastolic blood pressure, mmHg	81 (10)	78 (12)	<0.001	77 (10)	75 (12)	0.002
Hypertension	2054 (43.4%)	965 (18.2%)	<0.001	1960 (36.6%)	243 (16.0%)	<0.001
Treated hypertension[a]	680 (35.1%)	131 (13.6%)	<0.001	871 (45.9%)	25 (10.3%)	<0.001
High-density lipoprotein cholesterol, mg/dl	47 (12)	45 (15)	<0.001	56 (14)	52 (16)	<0.001
Low-density lipoprotein cholesterol, mg/dl	143 (37)	108 (40)	<0.001	140 (39)	113 (41)	<0.001
Triglycerides, mg/dl[b]	103 [77; 143]	132 [95; 194]	<0.001	83 [63; 115]	115 [86; 165]	<0.001
Total cholesterol, mg/dl	215 (41)	182 (49)	<0.001	217 (44)	188 (49)	<0.001
Treated dyslipidemia[c]	371 (7.90%)	18 (0.34%)	<0.001	437 (8.19%)	2 (0.13%)	<0.001
Glucose, mg/dl	104 (27)	97 (22)	<0.001	97 (23)	93 (22)	<0.001
Diabetes	730 (15.9%)	759 (14.3%)	0.029	592 (11.4%)	187 (12.3%)	0.354
Treated diabetes[d]	255 (35.8%)	69 (9.09%)	<0.001	186 (32.2%)	11 (5.88%)	<0.001
Body mass index, kg/m^2	27.5 (3.9)	24.0 (3.7)	<0.001	26.9 (5.1)	23.4 (4.5)	<0.001
Smoking	1559 (33.0%)	2430 (46.4%)	<0.001	987 (18.4%)	698 (46.5%)	<0.001
CAD risk[e]	3.9 [2.0; 7.2]	1.9 [1.1; 3.4]	<0.001	2.0 [0.8; 3.9]	0.7 [0.3; 1.4]	<0.001
Median follow-up[b]	13.3 [8.68; 15.0]	14.8 [10.2; 15.0]	<0.001	13.6 [10.0; 15.0]	15.0 [12.0; 15.0]	<0.001
All cause death	728 (15.2%)	1412 (26.6%)	<0.001	444 (8.18%)	294 (19.3%)	<0.001
Events at 15 years:			<0.001			<0.001
CAD	200 (4.18%)	165 (3.11%)		93 (1.71%)	13 (0.85%)	
Stroke	90 (1.88%)	65 (1.23%)		71 (1.31%)	9 (0.59%)	
Other causes death	639 (13.3%)	1321 (24.9%)		386 (7.11%)	289 (19.0%)	

CAD, coronary artery disease; PLWH, people living with HIV.
Values are expressed as mean (SD).
[a] Among patients with history of hypertension.
[b] Median (95% confidence interval).
[c] Among all cohort participants.
[d] Among patients with history of diabetes.

Table 2
Comparison of annual standardized incidence rates and 95% confidence intervals of coronary artery disease, stroke, and all-cause mortality per 100.000 inhabitants between women and men living with HIV and women and men from the general population in a 15-year follow-up.

	Coronary artery disease					
	Men			Women		
	General population	PLWH	*P*-value	General population	PLWH	*P*-value
25-54 years	205 [185-225]	279 [225-333]	0.006	57 [47-67]	82 [25-139]	0.199
55-74 years	582 [531-633]	652 [372-933]	0.315	..	..	..
	Stroke					
	Men			Women		
	General population	PLWH	*P*-value	General population	PLWH	*P*-value
25-54 years	58 [48-70]	106 [73-139]	0.004	31 [25-38]	39 [11-67]	0.307
55-74 years	338 [297-379]	292 [99-485]	0.325	..	..	..
	All-cause death					
	Men			Women		
	General population	PLWH	*P*-value	General population	PLWH	*P*-value
25-54 years	335 [309-360]	2005 [1875-2134]	<0.001	151 [135-168]	1476 [1264-1688]	<0.001
55-74 years	2898 [2774-3021]	4623 [3832-5414]	<0.001	..	..	..

The comparative analysis among women aged 55-74 years was not possible due to the limited sample size and the low number of events within this specific group. PLWH, people living with HIV.

Table 3
Hazard ratio and 95% confidence interval of CAD, stroke, and all-cause death for men and women with HIV in comparison with men and women from the general population (reference) by age groups.

	CAD		Stroke		All-cause death	
	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
25-54 years						
Men						
Adjusted for age	1.35 [1.00-1.83]	0.048	2.00 [1.18-3.40]	0.010	6.62 [5.44-8.05]	<0.001
Adjusted for risk factors[a]	1.33 [0.91-1.95]	0.141	1.53 [0.80-2.93]	0.197	3.08 [2.42-3.90]	<0.001
Women						
Adjusted for age	1.23 [0.59-2.59]	0.580	1.36 [0.54-3.42]	0.508	11.70 [8.64-15.85]	<0.001
Adjusted for risk factors[a]	0.35 [0.12-1.01]	0.051	1.33 [0.42-4.23]	0.634	4.71 [3.13-7.09]	<0.001
55-74 years						
Men						
Adjusted for age	1.07 [0.69-1.64]	0.773	0.97 [0.49-1.91]	0.921	2.32 [1.95-2.75]	<0.001
Adjusted for risk factors[a]	0.92 [0.53-1.62]	0.777	0.82 [0.33-2.00]	0.657	1.12 [0.86-1.44]	0.398

CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age, gender, systolic and diastolic pressure, total and high-density lipoprotein cholesterol, triglycerides, diabetes, and smoking. The comparative analysis of the models of incidence and all-cause mortality among women aged 55-74 years was not possible due to the limited sample size and the low number of events within this specific group.

other potential contributors (e.g., alcohol use, diet) was not available in our study.

The adjusted risk of CAD among PLWH was similar to that of the general population. These results are consistent with recent studies, which noted a decline in the association between HIV and cardiovascular events [16,33]. A study conducted by Klein et al. showed a non-statistically significant difference in the AMI risk among PLWH recruited between 2010 and 2011 compared with PLWH. In contrast, that risk was considerably higher for PLWH in earlier periods [16]. In addition, a recent study reported a non-significant association between PLWH and the risk of CAD [33]. However, contrary to our study, they observed a significantly higher risk of stroke in PLWH [33]. This is in sharp contrast with previous publications from the 90s or early 2000s, most of which have reported increased incidence of cardiovascular disease in men and women living with HIV compared with the general population [34–36]. Our cohort included patients recruited from 1995 onwards, spanning different ART eras. Therefore, our results cannot be directly compared with more recent cohorts exclusively exposed to contemporary ART. Although the fully adjusted models did not show statistically significant differences, the increased CAD risk observed in men with HIV younger than 55 years may indicate a clinically relevant signal that warrants further investigation. Furthermore, the general decrease in CAD and stroke among PLWH over time may be partially explained by modern ART, especially integrase strand transfer inhibitors are more lipid-friendly, and improved lipid management by HIV care providers, basically broader and earlier use of lipid-lowering therapies, especially statins.

The greater all-cause mortality in our PLWH cohort is consistent with a recent study on life expectancy in PLWH, where the authors emphasized that despite long-term ART, a shorter life expectancy persists among PLWH in high-income countries [2]. The finding of higher mortality among PLWH may be dependent on the nadir CD4 count of the population and on the absence of cancer screening programs for this specific population. With the exception of anal cancer, there are no systematic approaches for cancer diagnosis in PLWH, especially lung cancer, one of the most frequent in heavy smoker populations [30,31]. We did not have consistent data on nadir CD4 counts or systematic cancer screening practices. Nevertheless, our findings of higher non-cardiovascular mortality suggest that future research should explore these factors. In addition, the increased adjusted all-cause mortality risk in PLWH highlights the need for orienting health care strategies not only to cardiovascular disease prevention, but also to the specific causes of death in this population.

We cannot discard those other important factors not measured in our study, such as socioeconomic factors and stigma surrounding their HIV status, which may also be contributing to the increased non-cardiovascular cause mortality. The ensemble of these factors may also be influencing PLWH's overall quality of life.

This study has many strengths. First, its large sample size and 15-year follow-up enhance the statistical power and reliability of the findings. Second, age-standardization was used to analyze the incidence of CAD, stroke and all-cause mortality, ensuring harmonization and comparability across the cohorts. Third, the inclusion of gender and age-stratified data offers a comprehensive understanding of potential disparities. Last, adjusting for potential confounders strengthens the validity of the observed associations. The study also has some limitations that should be considered. First, the presence of missing data and a significant number of exclusions due to incomplete follow-up of PLWH might have introduced some bias, as there was a slightly different cardiovascular risk profile between included and excluded PLWH. However, despite the sample size loss, the study still maintains sufficient statistical power to ensure the reliability of its results. In addition, differences in recruitment and follow-up periods between cohorts, including the potential influence of COVID-19 mortality in 2020-2022, could have affected outcomes. Second, baseline risk factors, including smoking, blood pressure, and lipid profile, were measured only once at study entry and may have changed over time; this is a limitation of our analysis. Third, the study was conducted exclusively with Spanish cohorts, which could hamper its extrapolation to other populations or geographic regions, especially the REGICOR cohort that represents the Girona province and may not be fully generalizable to the entire Spanish population. Fourth, differences in baseline age distribution between cohorts may compromise direct comparability, even after age-standardization. Fifth, cholesterol and glucose were measured with different methods across cohorts, which may have introduced measurement heterogeneity. Sixth, we lacked data on ART regimens, viral suppression, and statin use, which limits the interpretation of some findings. Finally, we cannot discard that some residual confounding may persist despite model adjustment for measured potential confounding factors.

In conclusion, our study showed that despite a significantly higher crude incidence rate of CAD and stroke in men with HIV younger than 55 years, after adjustment for potential confounders, the risk of those diseases is similar to that of the general population. However, young PLWH exhibit more than three times the adjusted risk of all-cause mortality than the general population,

suggesting competitive causes of mortality in younger patients being responsible for their attenuated incidence of cardiovascular diseases at older age.

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Author contributions

Anna Camps-Vilaró, Ramon Teira, Irene R. Degano, Isaac Subirana, and Jaume Marrugat: Conceptualization. Anna Camps-Vilaró, Irene R. Degano, Isaac Subirana, and Jaume Marrugat: Methodology. Anna Camps-Vilaró, Isaac Subirana: Formal analysis. Anna Camps-Vilaró, Ramon Teira, Pere Domingo, Adrià Curran, Maria José Galindo, Marta Montero-Alonso, and Alberto Romero: Investigation. Ramon Teira, Pere Domingo, Adrià Curran, Maria José Galindo, Marta Montero-Alonso, Alberto Romero, and Jaume Marrugat: Resources. Anna Camps-Vilaró, Isaac Subirana: Data curation. Anna Camps-Vilaró: Writing—original draft preparation. Ramon Teira, Irene R. Degano, and Jaume Marrugat: Writing—review and editing. Anna Camps-Vilaró: Visualization. Ramon Teira, Irene R. Degano, and Jaume Marrugat: Supervision. Jaume Marrugat: Project administration. Ramon Teira, Pere Domingo, and Jaume Marrugat: Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Data sharing

The data that support the findings of this study are available from the corresponding authors, ACV and JM, upon reasonable request.

Declaration of competing interest

The authors have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108061.

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