Incidence of cardiometabolic diseases in people living with and without HIV in the UK: a population-based matched cohort study

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Brief summary: Comparing people with HIV (PWH) to matched people without HIV over a 20-year follow-up, we report an increased risk for composite cardiovascular disease, stroke, ischaemic heart disease, hypertension, type 2 diabetes, chronic kidney disease and all-cause mortality for PWH.

Abstract

Background:

Evidence on the risk of cardiovascular disease (CVD) and CVD risk factors in people with HIV (PWH) is limited. We aimed to identify the risk of composite CVD, individual CVD events and common risk factors.

Methods:

This was a nationwide population-based cohort study comparing adult (≥18y) PWH with HIV-negative individuals matched on age, sex, ethnicity and location. The primary outcome was composite CVD comprising stroke, myocardial infarction (MI), peripheral vascular disease (PVD), ischaemic heart disease and heart failure. The secondary outcomes were individual CVD events, hypertension, diabetes, chronic kidney disease (CKD) and all-cause mortality. Cox proportional hazard regression models were used to examine the risk of each outcome.

Results:

We identified 9233 PWH and 35721 HIV-negative individuals. An increased risk was found for composite CVD (adjusted hazard ratio [aHR] 1.50, 95% CI 1.28-1.77), stroke (aHR 1.42, 95% CI 1.08-1.86), ischaemic heart disease (aHR 1.55, 95% CI 1.24-1.94), hypertension (aHR 1.37, 95% CI 1.23-1.53), type 2 diabetes (aHR 1.28, 95% CI 1.09-1.50), CKD (aHR 2.42, 95% CI 1.98-2.94) and all-cause mortality (aHR 2.84, 95% CI (2.48-3.25).

Conclusions:

PWH have a heightened risk for CVD and common CVD risk factors, reinforcing the importance for regular screening for such conditions.

Keywords: HIV, cardiovascular disease, stroke, peripheral vascular disease, ischaemic heart disease, myocardial infarction, heart failure, hypertension, diabetes, chronic kidney disease

Background

The expansion of access to antiretroviral therapy (ART) has substantially reduced AIDS-related mortality [1]. Subsequently, non-AIDS-related causes of death in people with HIV (PWH) has increased, such as causes due to cardiovascular disease (CVD) [1]. Previous estimates suggest that PWH have a 2-fold risk for developing CVD compared to their HIV-negative counterparts; though, most studies were conducted over a decade ago [2]. CVD risk may have changed over the last decade due to better management of common CVD risk factors in PWH [3, 4], earlier initiation of ART [5] and reduced toxicity of ART [6]. Thus, evidence on the current overall risk of CVD is unknown.

The relationship between CVD and HIV is complex and poorly understood [6]. Various HIV and non-HIV mechanisms may contribute to PWH's susceptibility of CVD and may lead to varying risks for individual CVD events [6]. Most studies that report the risk of CVD events in PWH were conducted in the US, where healthcare access and health-seeking behaviours differ from other countries, including the UK where healthcare is free. For instance, a 2019 US study that investigated the risk of multiple CVD events in PWH used data from a large insurance database thus excluding uninsured individuals who are more deprived and vulnerable to CVD [7]. Similarly, the Veterans Aging Cohort Study (VACS) has investigated various CVD events [8-10]; however, this cohort of US veterans represent a more deprived older population with a high proportion of people from ethnic minority groups (70-80%) and few women (4%), limiting the generalisability of their results [8, 9, 11]. Studies conducted outside the US often suffer from design limitations, such as not controlling for key confounders (e.g. ethnicity) [12-14] and not matching the comparison group [12, 14]. Additionally, most studies focus on stroke, myocardial infarction (MI) and heart failure, thus limiting the evidence on other CVD events such as peripheral vascular disease (PVD) and ischaemic heart disease [6].

Our primary aim is to identify the risk of composite CVD in PWH, comprising stroke, PVD, ischaemic heart disease, MI and heart failure. Second, we aim to identify the risk of individual CVD events, all-cause mortality and common CVD risk factors including hypertension, type 2 diabetes and chronic kidney disease (CKD).

Methods

We report our study following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies [15]. Ethical approval was received by the Scientific Review Committee (reference number: 20SRC067).

Study design

We used a population-based matched cohort study design. The data was collected retrospectively; though, follow-up was done prospectively. Data was derived from The Health Improvement Network (THIN), a nationally representative UK-based anonymised database of primary care electronic records [16]. THIN data for diagnoses, lifestyle and anthropometric measurements have been considered well recorded and accurate [16, 17]. More than 90% of the UK population is registered with a general practice [18] and all general practices (n=808) available from THIN were included in our study. The study period was from 1st January 2000 to 1st January 2020.

Study population

All adults (≥18 years) with a first coded HIV diagnosis were eligible. The study entry began 12 months after registration with the general practice to ensure only incident outcome events of interest were captured; however, this may not have eliminated those with asymptomatic existing disease. The index date for PWH was the latest of the following: HIV diagnosis or one year after the registration date, the practice acceptable mortality recording date or the Vision IT system implementation date. Diagnoses before the study entry were considered prevalent HIV infections, and diagnoses after the study entry were considered incident HIV infections.

For each person with HIV, up to four individuals without HIV were matched based on region, sex, age within a one-year range and ethnicity. Criteria for matching was based on characteristics known to impact CVD risk in the general population [19]. Individuals without HIV were assigned the same index date as their matched counterpart.

Outcomes

The primary outcome of composite CVD included the first record of PVD, stroke, MI, ischaemic heart disease and heart failure; subsequent events were not considered. The individual CVDs were secondary outcomes along with all-cause mortality, hypertension, type 2 diabetes and CKD. CVD risk factors were chosen based on the literature and data availability. All conditions were identified by Read codes (supplementary table 1); Read codes were introduced in the UK National Health Service in 1985 and are checked for accuracy every 12 months [20]. All conditions were clinically diagnosed in primary or secondary care settings following national guidelines.

Follow-up

Follow up was from the index date until the exit date. Exit dates were calculated for each outcome of interest for each person and was the earliest date taken from the date of the outcome of interest, date they transferred out of the practice, date of death or study end date.

Covariates

Covariates were chosen based on existing literature regarding clinical importance and biological relevance and data availability [6]. Index year and age at index date were entered into all adjusted models as continuous variables. Sex (male and female), ethnicity (White, Black, Asian, Mixed race, and other), smoking status (current smoker, ex-smoker, and never smoked), body mass index (BMI) and social deprivation were entered as categorical covariates. BMI was defined as kg/m^2 at study entry and classified using World Health Organization criteria as follows: underweight (BMI of <18·5 kg/m^2), normal weight (BMI of 18·5 kg/m^2 to <25 kg/m^2), overweight (BMI of 25 kg/m^2 to <30 kg/m^2) and obesity class I, II, and III were combined (BMI of ≥30 kg/m^2) [21]. Townsend scores were used as a proxy for social deprivation; they are calculated based on employment, overcrowding (person per room in a household), car ownership and house ownership [22]. The 1st quintile of Townsend scores represent the least deprived individuals and the 5th quintile represents the most deprived individuals. Baseline data for hypertension, type 1 or 2 diabetes, CKD, PVD, stroke, MI, ischaemic heart disease and heart failure were also included as categorical covariates where appropriate. ART status, ART classification nor CD4 count data were available through THIN and therefore not included as covariates.

Statistical methods

All analyses were conducted in Stata 14.0 (College Station, Texas, USA). Descriptive statistics were used for reporting baseline data; presenting means for continuous variables and proportions for categorical variables. Cox proportional hazard regression models were used to calculate crude and adjusted hazard ratios (aHRs). A fitness test using Schoenfeld residuals methods identified three covariates that violated the proportional hazard assumption: age, ethnicity and smoking status. Due to the strong relationship between these covariates and CVD risk [23], they remained in the final model. Explorative models stratified by ethnicity and smoking status did not alter the final results. Each model included prevalent and incident HIV infections. Participants with CVD at baseline were excluded from the model investigating the risk of composite CVD; however, they were retained for outcomes of hypertension, diabetes, CKD and all-cause mortality. Similarly, participants with the outcome of interest at baseline were excluded for all other outcomes (e.g. those with stroke at baseline were excluded when investigating the risk for stroke). Subsequently, the baseline data relating to the outcome of interest was not entered as a covariate. Twenty multiple imputations by chained equations were used to impute missing data for BMI, smoking status, ethnicity and Townsend. A missing indicator was added to adjusted regressions for ethnicity due to the likeliness that missing was not at random [24].

Sensitivity analysis

To assess for potential effects of bias caused by prevalent HIV infections, a sensitivity analysis was conducted among incident HIV infections only using Cox proportional hazard regression models adjusted the same as the main analysis. Due to a high proportion of missing data for ethnicity, a sensitivity analysis was conducted for the primary outcome with records of missing ethnicity data excluded from the model.

Sub-group analysis

Sub-group analysis was undertaken for the following: age (<40 years old and ≥40 years old), sex (male and female), index year (2000 to 2009 and 2010 to 2019), smoking status (current or ex-smoker and never smoked), deprivation level (least deprived and most deprived), ethnicity (White and non-White ethnic groups) and BMI (<30 kg/m^2 and ≥30 kg/m^2). Hazard ratios with 95% CIs are presented for each sub-group between people with and without HIV. Incident and prevalent infections were included.

All statistical tests were two-tailed and a P <0.05 was considered statistically significant.

Results

From January 2000 to January 2020, 9233 PWH and 36816 people without HIV were identified (table 1). Age, sex and ethnicity were similar between the two groups by design: mean age was 41 years (standard deviation = 11), 34% were female, 37% were White, 22% were Black, 1% were Asian, 2% were of Mixed ethnicity, 2% were of other ethnicity and 36% were missing ethnicity data. Twenty-three percent of PWH were in the most deprived quintile compared to 15% of people without HIV. Thirty-six percent of PWH and 46% of people without HIV were either overweight or obese. People without HIV had a higher proportion of people that reportedly never smoked (49% vs 55%), and PWH had a higher proportion of current smokers (30% vs 22%). The prevalence of PVD, stroke, MI, ischaemic heart disease, heart failure and CKD at baseline was higher in PWH whereas prevalence of hypertension and diabetes was higher in people without HIV; though all differences were small.

A total of 890 CVD events occurred (176 PVD, 310 strokes, 242 MIs, 453 ischaemic heart disease, 190 heart failures) during the study period (table 2). Incident rates for all primary and secondary outcomes were higher for PWH.

Cardiovascular disease

HIV infection was associated with an increased risk of CVD, with an HR of 1.50 (95% CI 1.28-1.77) after adjusting for age, sex, BMI, ethnicity, smoking status, deprivation, index year and baseline events for hypertension, diabetes and CKD (table 2). The risk remained when prevalent infections were removed (supplementary table 2) and when those without ethnicity data were removed from the model (data not shown). HIV infection was associated with an increased risk of stroke and ischaemic heart disease in all models, with a 42% (aHR 1.42, 95% CI 1.08-1.86) and 55% (aHR 1.55, 95% CI 1.24-1.94) higher risk after adjustment, respectively. HIV infection was not associated with an increased risk for PVD, MI nor heart failure in any of the models (aHRs of 1.32 [95% CI 0.91-1.91]; 1.30 [95% CI 0.94-1.79]; 1.32 [95% CI 0.92-1.89], respectively).

Cardiovascular risk factors and all-cause mortality

PWH had more than a 2-fold increased risk for CKD and all-cause mortality compared to people without HIV (aHRs of 2.42 [95% CI 1.98-2.94] and 2.84 [95% CI 2.48-3.25], respectively) (table 2). HIV infection was associated with both type 2 diabetes and hypertension (aHR of 1.28 [95% CI 1.09-1.50] and 1.37 [95% CI 1.23-1.53], respectively). In the sensitivity analysis, the risk of PWH developing CKD and all-cause mortality increased to a 3-fold risk and remained significant (supplementary table 2). The risk of type 2 diabetes was no longer significant; however, the risk for hypertension remained unchanged and significant.

Sub-group analysis

Adjusted hazard ratios for the sub group analyses are presented with 95% CIs in table 3 (composite and individual CVDs) and table 4 (CV risk factors and all-cause mortality). Here we present a summary of the findings.

In both males and females, HIV infection was associated with an increased risk for composite CVD (47% and 60% respectively). Males with HIV had a 43% higher risk for stroke and a 47% higher risk for ischaemic heart disease whereas females had an 82% increased risk for ischaemic heart disease. Younger (<40y) and older (≥40) PWH had a 50% heightened risk for composite CVD compared to their uninfected counterparts. Older PWH (≥40y) had a 41% increased risk for stroke and 47% increased risk for ischaemic heart disease whereas younger (<40y) PWH had 2-times the risk for ischaemic heart disease and heart failure. Non-White PWH were not at a heighted risk for composite CVD, but had an 87% increased risk for stroke. White PWH had a 52% increased risk for composite CVD, and a 69% and 58% increased risk for MI and ischaemic heart disease, respectively. The association between HIV infection and CVD did not differ by deprivation status. No difference was found between obese individuals with and without HIV in the risk for composite or singular CVD. However, non-obese individuals with HIV were associated with a 53% increased risk of composite CVD, driven by a 62% increased risk for ischaemic heart disease. PWH that have never smoked or are current or ex-smokers had a 43% and 45% increased risk of composite CVD, and a 63% and 45% increased risk for ischaemic heart disease, respectively. HIV infection was associated with a 51% and 49% increased risk for composite CVD in the earlier index years (2000-2009) and later years (2010-2019), respectively. The earlier index years also resulted in a 68% heightened risk for ischaemic heart disease.

In all sub-groups, PWH had a significantly higher risk of all-cause mortality and CKD. Compared to their uninfected counterparts, the following groups of PWH had an increased risk for type 2 diabetes: males, those aged 40 years or older, least deprived, non-obese, never smoked and those

with an earlier index date (2000-2009). All groups, aside from the least deprived individuals and obese PWH, were at a heightened risk for hypertension compared to their HIV-negative counterparts.

Discussion

As the life expectancy of PLWH continues to increase, understanding their risk of age-related conditions is imperative for reducing excess morbidity and mortality. Our results demonstrate that PWH are at a heightened risk for CVD, particularly for stroke and ischaemic heart disease. We found no elevated risk for PVD, MI nor heart failure. We presented evidence on the risk of common CVD risk factors, highlighting an association between HIV infection and incident hypertension, type 2 diabetes and CKD. Additionally, we reported a nearly 3-fold risk for all-cause mortality. The risk of individual CVD events and CVD risk factors varied across key demographics, including age, sex and ethnicity.

Our study results are in line with previous evidence [2], confirming a sustained increased risk for composite CVD. This increased risk could be due to increased awareness of CVD in PWH and subsequently improved screening within this population. Another plausible cause is exposure to ART. ART has been found to decrease CVD risk by immune regulation and viral suppression; however, ART also increases the risk as a result of changes to lipid levels and metabolic profiles [6, 25]. The relationship between ART and CVD is complex and long-term effects are unclear [6, 25, 26]. Whilst the current study was unable to control for ART, the risk remained the same in earlier (2000-2009) and later (2010-2019) index years. Initiation of ART has increased to 90% in the UK over the last decade [27], though this sub-group analysis indicates that CVD risk may not be impacted by improved ART coverage. However, more longitudinal studies are needed to distinguish the true

impact of ART on CVD risk. Other key confounders such as age and smoking did not impact the risk of CVD in our study. The increased risk we report may therefore be due to other HIV-related mechanisms such as persistent immune activation and inflammation caused from the presence of HIV viraemia and microbial translocation which occurs regardless of treatment status [28].

In accordance to other studies, we found an increased risk for stroke. However, our findings indicate a lower risk than the 2-fold risk reported in a 2018 meta-analysis, which is likely inflated due to the high-risk populations reviewed [2]. Two separate studies reported a 2- and 3-fold risk for stroke [7, 30]; however, ethnicity was not controlled for which is a known confounder. Three studies that were powered and matched by age, sex and ethnicity reported significant effect sizes in line with ours (HRs of 1.93, 1.17, and 1.21), despite being carried out in the US and not being population-based [9, 31, 32]. We reported a 55% increased risk for ischaemic heart disease; though, there was no risk for MI. This could be due to a lack of power as the overall effect size was still large (30%) along with many of the sub-groups for this outcome (i.e. females). Two 2019 meta-analyses report a 73 to 96% increased risk for MI in PWH [33, 34]. To our knowledge, no study has investigated the relative risk of incident ischaemic heart disease, indicating the need for future studies to confirm these important findings and examine the role MI plays within this risk.

Inconsistent with other studies investigating heart failure, we found no increased risk for this outcome. The two most recent studies (2019 and 2018) found more than a 2-fold risk [7, 35], a finding we reported only in younger (<40y) PWH. Similar to MI, the insignificant finding for heart failure could be due to a lack of power as the effect size was large (32%). The same is true for PVD (32%). None of the sub-groups were at an increased risk for PVD; however, a downward trend in risk is indicative when comparing the later (2010-2019) and earlier index years (2000-2009). Evidence on PVD risk is limited and inconclusive [6]. A VACS study found a 19% increased risk in PVD [8] whereas two other large studies [7, 14] reported no increased risk. Further research is needed to understand the true risk of PVD and how this has changed over time.

We confirmed that people with HIV are at a heightened risk for hypertension, type 2 diabetes, CKD and all-cause mortality. Nearly all sub-groups were at twice the risk for CKD; however, those younger than 40 had 4-times the risk and the risk was 3-fold in the later index years (2010-2019). Similarly, those younger than 40 and those with a later index year (2010-2019) were at a 6-times and 3-times risk for all-cause mortality, respectively. Additionally, the least deprived PWH had a 4-fold risk of all-cause mortality. These are important findings for understanding who should be prioritised in future research and targeted in prevention programmes. Despite hypertension, type 2 diabetes and CKD having minimal impact on the risk of CVD in our study, it is clear that screening of such CVD risk factors should be a priority. Annual screening for common CVD risk factors is recommended by the British HIV Association [36]. However, compared to other European studies [37, 38], the incidence for risk factors in the current study are lower which may indicate underdiagnosis of important CVD risk factors in PWH in the UK. Guidelines also advise for an annual CVD risk assessment for those older than 40 or if they have significant CVD risk factors [36]. However, the CVD risk assessment tool used in the UK (QRISK) has not been validated in PWH, and likely underestimates their true risk [36]. From our findings, we know PWH are at high risk for CVD, irrespective of their sex, age and smoking status. Therefore, regardless of CVD status and risk score, annual screening for CV risk factors and disease should be considered and trialled in future studies.

The large population-based matched cohort used for our study is a notable strength. This allowed us to look at composite CVD, individual CVD events, common risk factors, the risk of each across key sub-groups and compare the risk to an HIV-negative population. Few studies have reported the risk of composite CVD and many suffer from design limitations; therefore, our robust study enhances the current evidence on the risk of CVD in PWH. Though, there are some limitations to mention. One key limitation is the absence of data relating to treatment status, ART regimens used, duration of treatment and CD4 T-cell counts, all of which have been shown to impact the risk of CVD [6]. This lack of data limits the interpretations possible from our findings. Further to this, some effect sizes reported for our secondary outcomes, sensitivity analysis and sub-group analysis are large but were

found insignificant, which may indicate a lack of power for some of the outcomes. These results should therefore be interpreted with caution. Uncontrolled confounding is likely to remain, despite matching and adjusting for important covariates.

In conclusion, PWH remain at a heightened risk for CVD, specifically stroke and ischaemic heart disease. An elevated risk was also found for hypertension, type 2 diabetes, CKD and all-cause mortality. These risks differed across key demographics such as age, sex and ethnicity; indicating who to target in future research and prevention strategies. Our results reiterate the importance of regular screening for CV risk factors and disease in PWH. However, common CVD risk factors had little impact on the overall risk of CVD, hence, an HIV-validated risk assessment tool and further investigation into who should receive regular assessments would be beneficial. Additional research is needed to ascertain the mechanisms behind the risk of individual CVD events. A better understanding of contributing factors could aid in reducing the excess morbidity and mortality caused by CV risk factors and disease in PWH.

Footnotes

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Conflict of interest

KJ is part funded by the National Institute for Health Research (NIHR) Applied Research Centre (ARC) West Midlands. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. DAL has received investigator-initiated educational grants from Bristol-Myers Squibb (BMS), has been a speaker for Boehringer Ingeheim, Bayer, and BMS/Pfizer and has consulted for BMS, Boehringer Ingelheim, and Daiichi-Sankyo, all outside the current work. Authors have no other conflict of interests to disclose.

A preliminary abstract was awarded an oral presentation at the virtual 11th International AIDS Society Conference on HIV Science in July 2021.

Data sharing

THIN data governance does not allow us to share individual patient data, and therefore, only metadata are presented. Researchers may apply for individual patient data access at https://www.iqvia.com/solutions/real-world-value-and-outcomes (contact tab).

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Table 1. Baseline demographics; figures are N (%) unless otherwise stated.

	People with HIV (n=9233)	People without HIV (n=36816)
Age at index date		
Mean (standard deviation)	41.0 (11.0)	41.0 (11.0)
Sex		
Female	3172 (34.4)	12598 (34.2)
Ethnicity		
White	3424 (37.1)	13695 (37.2)
Black	2080 (22.5)	8243 (22.4)
Asian	89 (1.0)	352 (1.0)
Mixed	153 (1.7)	611 (1.7)
Other	174 (1.9)	667 (1.8)
Missing	3313 (35.9)	13248 (36.0)
Townsend / deprivation quintile		
1st quintile (least deprived)	700 (7.6)	5564 (15.1)
2nd quintile	880 (9.5)	5262 (14.3)
3rd quintile	1312 (14.2)	6347 (17.2)
4th quintile	1740 (18.9)	6325 (17.2)
5th quintile (most deprived)	2155 (23.3)	5649 (15.3)
Missing	2446 (26.5)	7669 (20.8)
Body mass index		
Underweight (<18.5 kg/m^2)	307 (3.3)	614 (1.7)
Normal weight (18.5 kg/m^2 to <25 kg/m^2)	3567 (38.6)	11317 (30.7)
Overweight (25 kg/m^2 to <30 kg/m^2)	2143 (23.2)	10146 (27.6)
Obese (≥30 kg/m^2)	1152 (12.5)	6726 (18.3)
Missing	2064 (22.4)	8013 (21.8)
Smoking status		
Current smoker	2750 (29.8)	8132 (22.1)
Ex-smoker	1292 (14.0)	5456 (14.8)

Never smoked	4499 (48.7)	20390 (55.4)
Missing	692 (7.5)	2838 (7.7)
Comorbidities		
Composite CVD[a]	353 (3.8)	939 (2.6)
Peripheral vascular disease	48 (0.5)	143 (0.4)
Stroke	152 (1.7)	311 (0.8)
Myocardial infarction	102 (1.1)	243 (0.7)
Ischemic heart disease	174 (1.9)	541 (1.5)
Heart failure	49 (0.5)	99 (0.3)
Hypertension	713 (7.7)	3200 (8.7)
Diabetes (type 1 and type 2)	307 (3.3)	1257 (3.4)
Chronic kidney disease	98 (1.1)	258 (0.7)

[a] Composite cardiovascular disease (CVD) comprises peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease and heart failure.

Table 2. Study characteristics, incident rates and hazard ratios for each outcome.

	Number of individuals[a] *N*		**Number of events** *N (%)*[b]		**Incident rates (IR)** *IR per 1000 person-years*		**Person years** *Total person years*		**Crude Hazard Ratio** *Crude HR (95% CI)*	**Adjusted Hazard Ratio**[c] *Adjusted HR (95% CI)*
	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV	People without HIV	People with HIV vs People without HIV	People with HIV vs People without HIV
Composite CVD[d]	8880	35877	207 (2.3)	683 (1.9)	5.33	3.69	38814.8	184877.8	1.49 (1.27, 1.74) **	1.50 (1.28, 1.77) **
Peripheral vascular disease	9185	36673	39 (0.4)	137 (0.4)	0.96	0.72	40719.3	191012.5	1.37 (0.96, 1.95)	1.32 (0.91, 1.91)
Stroke	9081	36505	72 (0.8)	238 (0.7)	1.79	1.25	40205.1	189856.1	1.47 (1.13, 1.92) **	1.42 (1.08, 1.86) *
Myocardial infarction	9131	36573	51 (0.6)	191 (0.5)	1.26	1.00	40440.0	190268.5	1.29 (0.95, 1.76)	1.30 (0.94, 1.79)
Ischaemic heart disease	9059	36275	108 (1.2)	345 (1.0)	2.71	1.84	39911.4	187995.5	1.52 (1.22, 1.89) **	1.55 (1.24, 1.94) **
Heart failure	9184	36717	42 (0.5)	148 (0.4)	1.03	0.77	40750.5	191305.1	1.36 (0.96, 1.91)	1.32 (0.92, 1.89)
Hypertension	8520	33616	456 (5.4)	1666 (5.0)	12.70	9.93	35911.6	167722.7	1.30 (1.17, 1.44) **	1.37 (1.23, 1.53) **
Type 2 diabetes	8926	35559	197 (2.2)	862 (2.4)	5.06	4.72	38940.8	182682.4	1.09 (0.93, 1.27)	1.28 (1.09, 1.50) **

Chronic kidney disease	9135	36558	160 (1.8)	337 (0.9)	3.99	1.78	40065.2	189728.9	2.32 (1.92, 2.80) **	2.42 (1.98, 2.94) **
All-cause mortality	9233	36816	384 (4.2)	559 (1.5)	9.35	2.91	41059.2	192215.8	3.25 (2.85, 3.70) **	2.84 (2.48, 3.25) **

[a] The number of participants will differ for each outcome. This is due to the exclusion of participants that already had the outcome at baseline.

[b] Percentages correspond with the number of events (numerator) and the number of individuals for that particular group (denominator) within the corresponding row.

[c] Adjusted for age, body mass index, sex, smoking status, ethnicity, deprivation, index year and events at baseline.

[d] Composite cardiovascular disease (CVD) comprises peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease and heart failure events.

* P-value <0.05.

** P-value <0.01.

Table 3. Sub group analysis[a] for composite and individual CVDs; adjusted hazard ratios for people with HIV compared to people without HIV, with 95% CIs presented.

	Composite CVD[b]	Peripheral vascular disease	Stroke	Myocardial infarction	Ischaemic heart disease	Heart failure
Sex						
Male	1.47 (1.22, 1.76) **	1.36 (0.91, 2.03)	1.43 (1.04, 1.97) *	1.19 (0.84, 1.70)	1.47 (1.15, 1.89) **	1.19 (0.78, 1.81)
Female	1.60 (1.12, 2.29) *	1.02 (0.36, 2.90)	1.49 (0.85, 2.61)	2.15 (0.96, 4.80)	1.82 (1.04, 3.20) *	1.80 (0.89, 3.67)
Age						
<40 years old	1.50 (1.01, 2.24) *	0.37 (0.05, 2.87)	1.40 (0.73, 2.71)	1.64 (0.76, 3.54)	2.08 (1.15, 3.77) *	2.42 (1.12, 5.22) *
≥ 40 years old	1.50 (1.26, 1.79) **	1.41 (0.96, 2.06)	1.41 (1.04, 1.91) *	1.23 (0.86, 1.75)	1.47 (1.15, 1.88) **	1.12 (0.74, 1.69)
Ethnicity						
Non-White[c]	1.34 (0.89, 2.02)	1.07 (0.18, 6.21)	1.87 (1.05, 3.36) *	0.76 (0.25, 2.27)	1.25 (0.65, 2.41)	1.12 (0.51, 2.44)
White	1.52 (1.20, 1.94) **	1.34 (0.77, 2.32)	1.23 (0.81, 1.87)	1.69 (1.07, 2.67) *	1.58 (1.13, 2.23) **	1.27 (0.73, 2.22)
Deprivation						
Most deprived	1.24 (0.86, 1.79)	1.13 (0.50, 2.55)	1.38 (0.77, 2.46)	1.43 (0.67, 3.02)	1.44 (0.84, 2.45)	0.88 (0.42, 1.85)
Least deprived	1.25 (0.74, 2.10)	0.87 (0.24, 3.17)	1.40 (0.58, 3.38)	1.67 (0.68, 4.10)	1.28 (0.62, 2.64)	0.52 (0.07, 4.12)
Body mass index						
Obese	1.30 (0.88, 1.92)	1.28 (0.55, 3.01)	1.65 (0.88, 3.09)	0.77 (0.31, 1.96)	1.35 (0.79, 2.31)	0.76 (0.34, 1.68)
Not Obese	1.53 (1.25, 1.88) **	1.34 (0.84, 2.15)	1.36 (0.95, 1.95)	1.38 (0.94, 2.03)	1.62 (1.24, 2.13) **	1.32 (0.81, 2.15)

Smoker status						
Current or ex-smoker	1.45 (1.16, 1.80) **	1.11 (0.71, 1.75)	1.36 (0.92, 2.00)	1.27 (0.85, 1.90)	1.45 (1.08, 1.96) *	1.49 (0.92, 2.41)
Never smoked	1.43 (1.09, 1.88) *	1.74 (0.80, 3.81)	1.38 (0.89, 2.13)	1.39 (0.76, 2.54)	1.63 (1.11, 2.40) *	1.27 (0.72, 2.26)
Index year						
2000-2009	1.51 (1.24, 1.86) **	1.51 (0.96, 2.38)	1.35 (0.96, 1.91)	1.28 (0.85, 1.92)	1.68 (1.28, 2.21) **	1.21 (0.75, 1.96)
2010-2019	1.49 (1.14, 1.95) **	0.96 (0.50, 1.87)	1.58 (1.00, 2.50)	1.32 (0.76, 2.24)	1.32 (0.88, 1.97)	1.41 (0.82, 2.42)

[a] Adjusted for age, body mass index, sex, smoking status, ethnicity, deprivation, index year and events at baseline.

[b] Composite cardiovascular disease (CVD) comprises peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease and heart failure events.

[c] Non-White sub-group includes people that identify as Black, Asian, Mixed or other.

* P-value <0.05.

** P-value <0.01.

Table 4. Sub group analysis[a] for CVD risk factors and all-cause mortality; adjusted hazard ratios for people with HIV compared to people without HIV, with 95% CIs presented.

	Hypertension	Type 2 diabetes	Chronic kidney disease	All-cause mortality
Sex				
Male	1.42 (1.25, 1.61) **	1.33 (1.09, 1.61) **	2.60 (2.03, 3.32) **	2.88 (2.46, 3.37) **
Female	1.28 (1.05, 1.56) *	1.13 (0.85, 1.51)	2.10 (1.50, 2.95) **	2.91 (2.20, 3.85) **
Age				
<40 years	1.57 (1.27, 1.93) **	1.22 (0.85, 1.76)	4.67 (2.54, 8.58) **	6.73 (4.91, 9.21) **
≥ 40 years	1.34 (1.18, 1.52) **	1.29 (1.08, 1.54) **	2.28 (1.84, 2.81) **	2.27 (1.94, 2.66) **
Ethnicity				
Non-White[b]	1.37 (1.22, 1.66) **	1.23 (0.94, 1.61)	1.56 (1.04, 2.36) *	3.44 (2.35, 5.03) **
White	1.28 (1.07, 1.52) **	1.16 (0.87, 1.53)	2.88 (2.09, 3.98) **	2.33 (1.85, 2.94) **
Deprivation				
Most deprived	1.32 (1.05, 1.66) *	1.27 (0.92, 1.76)	1.71 (1.07, 2.72) *	2.45 (1.85, 3.23) **
Least deprived	1.11 (0.76, 1.62)	1.72 (1.04, 2.87) *	2.29 (1.29, 4.04) **	4.85 (3.12, 7.54) **
Body mass index				
Obese	1.10 (0.87, 1.39)	1.03 (0.79, 1.35)	2.17 (1.42, 3.30) **	2.07 (1.41, 3.05) **
Not Obese	1.38 (1.20, 1.59) **	1.46 (1.16, 1.85) **	2.33 (1.81, 3.00) **	2.95 (2.49, 3.49) **
Smoker status				

Current or ex-smoker	1.19 (1.00, 1.42) *	1.27 (0.99, 1.63)	2.77 (2.05, 3.76) **	2.68 (2.23, 3.21) **
Never smoked	1.54 (1.33, 1.78) **	1.32 (1.06, 1.65) *	2.17 (1.64, 2.88) **	2.70 (2.12, 3.43) **
Index year				
2000-2009	1.34 (1.17, 1.53) **	1.40 (1.14, 1.71) **	2.08 (1.63, 2.65) **	2.75 (2.33, 3.25) **
2010-2019	1.45 (1.21, 1.75) **	1.09 (0.84, 1.42)	3.35 (2.37, 4.74) **	3.01 (2.37, 3.82) **

[a] Incident HIV infections only, adjusted for age, body mass index, sex, smoking status, ethnicity, deprivation, index year and all outcomes of interest at baseline.

[b] Non-White sub-group includes people that identify as Black, Asian, Mixed or other.

* P-value <0.05.

** P-value <0.01.