Comorbid diseases and conditions in people with human immunodeficiency virus

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Abstract

Objectives: This paper aims to identify and characterise the risk of progressing to pre-specified comorbidities in people living with HIV (PLHIV) compared with a matched HIV-negative population.

Methods: Primary and secondary care records from the Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics (HES) was used to identify PLHIV and their matched HIV-negative control. Survival analysis techniques were used to determine the risk of developing certain comorbidities of interest which included central nervous system (CNS) disorders as well as end-stage renal disease, osteoporosis, diabetes, cardiovascular disease (CVD), hypertension, stroke, and cancer.

Results: 2,945 PLHIV were matched to 5,890 HIV-negative controls. PLHIV had a significant increased hazard ratio for time to the development of first sleep disorders, depression, osteoporosis, stroke, cancer and end stage renal disease when compared to their matched HIV-negative control. The hazard ratios for anxiety, hypertension, diabetes, and CVD were not significantly increased.

Conclusion: PLHIV are at a higher risk of developing certain comorbid conditions highlighting the need for PLHIV to have annual health reviews to monitor the development of comorbidities in line with the British HIV Associations (BHIVA) quality standard for care.

Introduction

Human immunodeficiency virus (HIV) affects over 37 million people worldwide[1]. HIV infection is characterised primarily by the progressive loss of CD4^{+} T cells[2], leading to immunodeficiency and associated complications, including opportunistic infections and malignancies[3]. Late presentation of HIV contributes to a higher risk of HIV-related mortality. A large proportion of patients are diagnosed only following presentation with complications of HIV, sometimes too advanced to be reversed. A long-term retrospective cohort study in a high-middle income country found that 45% of patients diagnosed with HIV developed AIDS within a year of their diagnosis[4]. Antiretroviral therapies have revolutionised HIV treatment, improving survival and reducing complications, although they are not curative[5]. HIV infection itself, and adverse effects of some antiretroviral drug therapies, increase the risk of various comorbidities including cardiovascular disease (CVD), kidney disease, type 2 diabetes (T2DM), liver disease, and osteoporosis.

CVD represents one of the leading causes of death in HIV-positive people, and it has been estimated that by 2030, 78% of people living with HIV (PLHIV) will experience CVD[6]. When compared with the general population, PLHIV have an increased risk of myocardial infarction and stroke, even after controlling for recognised cardiovascular risk factors[7,8]. Chronic kidney disease (CKD) and end-stage renal failure (ESRF) are also more common in PLHIV, with poorer clinical outcomes including increased mortality, compared to the HIV negative population[9]. The prevalence of kidney disease in PLHIV is expected to continue to rise due to their improved survival[10].

HIV-associated insulin resistance and treatment with combination antiretroviral therapy (cART) are believed to be the primary factors leading to an increased risk of T2DM in PLHIV. T2DM has been reported to be four times more common in HIV-positive men treated with cART compared with the HIV-negative population[11].

PLHIV have an increased risk of osteoporosis, low bone mineral density, and fractures. A systematic review and meta-analysis concluded that the risk of osteoporosis was greatest in individuals co-infected with HIV and hepatitis C, with a prevalence of osteoporosis of 22% in those co-infected individuals[12]. Liver disease is the second most common cause of mortality in HIV-infected patients. Liver damage in PLHIV may be a result of chronic hepatitis B or C co-infection, or of high reported chronic alcohol use (30%)[13].

An understanding of the evolving prevalence of HIV comorbidities will allow for more efficient allocation of clinical resources. The aim of this study was to characterise the PLHIV in the UK, and to identify and characterise their risk of progressing to pre-specified comorbidities compared with matched HIV-negative controls.

Methods

Data source

This study used data from the Clinical Practice Research Datalink (CPRD), in combination with linked Hospital Episode Statistics (HES) data. CPRD comprises pseudonymised data collected in an ongoing database from participating primary-care practices throughout the UK[14]. The CPRD database used for this study is CPRD GOLD, which is based on data collected through the Vision GP software. Patients records are flagged as being of acceptable research quality in CPRD if the patient in question has been permanently registered at the practice, and their records are 'up-to-standard' for research purposes.

This study was granted CPRD Independent Scientific Advisory Committee (ISAC) approval (protocol number: 18_226).

Patient identification

The study population were identified from permanently registered patients in CPRD GOLD, diagnosed with HIV 1st January 1988 to 31st December 2017, from primary care practices of acceptable research quality, who were eligible for linkage to HES. Index date was set to the earliest of a patients' documented HIV diagnosis based on Read codes or a positive HIV test result. Controls were assigned the index date of their matched counterpart. Cases were matched to HIV-negative controls on a 1:2 basis on age, gender and primary care practice. Patients were followed to the earliest of death, transfer out date, end of CPRD/HES record date, or 31st December 2017.

Statistical analysis

Demographic data are presented for both HIV-positive patients and their matched HIV-negative controls. Summary statistics (mean, standard deviation (SD)) are presented for continuous variables. Counts (n) and proportions (%) were presented for categorical variable. The number and proportions of missing data are reported as a separate category for each variable.

Kaplan Meier curves were produced for each comorbidity, to demonstrate time to diagnosis in the five years post index date. Patients with a prior history of the comorbidity of interest were excluded from the equivalent Kaplan Meier. The Chi-squared test statistic were produced using the log-rank test to assess differences between PLHIV and HIV-negative patients.

Cox proportional hazard models were generated to determine the risk of developing a given comorbidity and were presented in terms of hazard ratios (HR), 95% confidence intervals (CI), and p-values. Patients diagnosed with a comorbidity of interest on, or prior to their index date were excluded from each relevant comorbidity analyses, therefore the risk estimate was for incident diagnoses. Cox proportional hazard models were adjusted for age, gender and ethnicity.

Comorbidities of interest included central nervous system (CNS) disorders (sleep disorders, anxiety, and depression), as well as end-stage renal disease, osteoporosis, diabetes, CVD, hypertension, stroke, and cancer. Both Read codes and ICD-10 codes were used to identify patients with comorbidities of interest.

Results

Baseline characteristics

Overall there were 2,945 PLHIV who could be matched to 5,890 HIV-negative controls (ratio 1:2). PLHIV were matched to HIV-negative controls on their age and gender and therefore the mean age at baseline was 39.1 years (SD ± 12.7) and the proportion of males in each group was 65.9% for both populations (Table 1).

The proportions of patients within an ethnic group were significantly different between the two populations (p<0.0001), although this statistic may be influenced by the missing ethnic category. The ethnic group categories of highest proportion within PLHIV were White (45.4%), Black (26.1%), and missing (21.5%) whilst in the HIV-negative control group, they were White (53.9%), missing (31.6%), and Black (5.9%) (Table 1). Baseline mean body mass index (BMI) values were significantly lower within the HIV-positive population with a mean of 25.2 kg/m^2 (SD ± 5.4 kg/m^2) compared to 27.5 kg/m^2 (SD ± 6.1 kg/m^2) in the HIV-negative controls (p<0.0001) (Table 1).

At baseline, a significantly higher proportion of PLHIV had received a diagnosis of depression (21.9% vs 16.1%, p<0.0001), anxiety (9.8% vs 8.4%, p=0.0350), or sleep disorder (7.7% vs 4.6%, p<0.0001) compared with the HIV-negative control group (Table 1). In terms of non-CNS associated comorbidities at baseline, hypertension was the comorbidity reporting the highest proportion of patients within both the PLHIV and HIV-negative groups, affecting 7.4% and 7.1% of patients respectively (p=0.5703). When compared with the HIV-negative control group, higher proportions of PLHIV had a prior diagnosis of cancer (6.9% vs 2.8%,

p<0.0001), cardiovascular disease (4.5% vs 2.2%, p<0.0001), end-stage renal disease (2.3% vs 1.2%, p<0.0001), and stroke (1.1% vs 0.4%, p=0.0004), (Table 1). The number of patients available for each of the analyses can be found in Table 2.

Unadjusted analysis – Kaplan Meier

When considering the unadjusted time to event analysis, there was no significant difference in time to first anxiety diagnosis, renal disease and diabetes diagnosis between PLHIV and their controls. After five years, 9% (95% CI; 8%–11%) of HIV-negative patients had a diagnosis of depression, compared to 14% (12%–16%) of PLHIV (p<0.0001). Over the same time period 4% (3%–4%) of HIV-negative patients had a diagnosis of sleep disorders, and 7% (5%–7%) of PLHIV had a diagnosis of sleep disorder (p<0.0001). Differences were observed in the time to diagnosis with over the follow up period with 2% (2%–3%) of HIV-negative patients having a diagnosis at five years compared to 5% (4%–6%) (p <0.0001).

There was also a statistically significant difference for the time to first stroke, and osteoporosis for PLHIV compared to their matched controls. However, due to low numbers of events observed in these cohorts this statistical significance should be interpreted with caution.

Cox proportional hazard model

For each of the cox proportional hazard models, patients with a prior history of the disease of interest were removed from the cohort along with their matched control. The hazard ratios for sleep disorder (1.76; 95% CI 1.42-2.20; p<0.0001), depression (1.66; 95% CI 1.41-1.97; p<0.0001), osteoporosis (3.92; 95% CI 2.38-6.44; p<0.0001), stroke (2.14; 95% CI 1.39-3.30; p=0.0006), cancer (1.94; 95% CI 1.59-2.39; p<0.0001) and end stage renal disease (1.25; 95% CI 1.02-1.53; p=0.0340) were significantly increased for PLHIV, in comparison

with the HIV-negative controls. Hazard ratios for anxiety (HR 1.21; 95% CI 0.97-1.51; p=0.0826), hypertension (HR 1.05; 95% CI 0.87-1.26; p=0.6310), diabetes (HR 1.09; 95% CI 0.84-1.43; p=0.5098), and cardiovascular disease analyses (1.13; 95% CI 0.88-1.45; p=0.3396) were not significantly increased.

Discussion

A higher proportion of males than females were diagnosed within the HIV-positive population since gay and bisexual men (GBM; previously referred to as men who have sex with men) remained the highest risk group for HIV infection in the UK[15]. Our findings relating to ethnicity were probably influenced by the relative proportion of missing values. However, extracting the Black ethnic group category revealed a higher proportion for PLHIV (26.1%), compared with the HIV-negative control group (5.9%) (Table 1). People of Black-African ethnicity are known to bear a disproportionate burden of HIV infection, hence this was expected.[16] All Cox proportional hazard models were adjusted for ethnicity.

A higher proportion of PLHIV had been diagnosed with prior depression at baseline compared to their matched controls. For PLHIV, 22% of patients reported depression, which concurs with prior research reporting a 22% prevalence of depression within the HIV-positive population of Europe[17]. The hazard ratio for depression reported in this study was 1.66 (95% CI 1.41-1.97, p=<0.0001), reflecting an increased risk of depression in this group. The time to diagnosis of depression was also significantly shorter in PLHIV than their matched controls.

Prior anxiety was higher in PLHIV than in the control group, this increased risk was reflected post-baseline but not significantly (HR:1.21; 95% CI 0.97-1.51; p=0.0826). No difference was observed between groups in time to incident anxiety diagnosis. The prevalence of anxiety disorders within the HIV/AIDS population has been reported to be 23%, compared with 18% in the general population[18]. A systematic literature review by Chaponda et al also found that the prevalence of anxiety to be in the range of 22%-49% in PLHIV versus 4-5% in the general

population. [19] It is known that discrimination and stigma surrounding a HIV diagnosis can impact the mental health of PLHIV[20].

The proportion of patients with a prior history of sleep disorders was higher in PLHIV. This was also reflected in the post diagnosis period with a hazard ratio of 1.76 (95% CI 1.42 – 2.20, p=<0.0001). The prevalence of sleep disorders within the HIV-positive population has been reported to be as high as 70%[21]. These findings suggest that HIV-positive patients may require additional monitoring due to a higher risk of developing CNS comorbidities.

The proportion of patients with prior hypertension at baseline did not significantly differ between the two populations. The hazard ratio for the development of hypertension post baseline was not statistically significant (HR 1.05; 95% CI 0.87-1.26, p=0.6310). Previous data characterising the prevalence of hypertension within the HIV-positive population is inconclusive, with some studies reporting an increased pattern, and others reporting no increase[22].

The advent of cART has led to a decline in the risk of certain cancers among PLHIV, in particular AIDS-defining cancers, with the exception of invasive cervical cancer[23]. However effectively treated HIV-positive individuals are still at an increased risk of non-AIDS-defining cancers (NADCs)[24,31]. In our data, we observed an increased hazard ratio for cancer development in PLHIV (HR 1.94; 95% CI 1.59-2.39, p=<0.0001). However, a higher proportion of PLHIV also had a prior diagnosis of cancer at baseline, compared with the HIV-negative control group.

A higher proportion of PLHIV had a prior diagnosis of CVD compared with controls. However, the hazard ratio for the development of CVD did not show a significant increased risk of incident CVD (HR 1.13; 95% CI: 0.88 – 1.45, p=0.3396). Previous reports have suggested an increased prevalence of CVD within the HIV-positive population, owing to multitude of factors including treatment side-effects and high occurrence of traditional cardiovascular risk factors within the HIV-positive population[25]. In addition, people of black ethnicity are known to be at an increased risk of cardiovascular death[26]. Contrary to this, our model found that being of black ethnicity was a protective factor with people of black ethnicity being half as likely to develop CVD compared to people of white ethnicity (HR 0.49; 95% CI: 0.28-0.84; p=0.0095). However, our analysis may be highlighting a lack of reporting and early diagnosis of CVD in people of black ethnicity, which may subsequently be contributing to an increase in CVD deaths observed in this population.

Stroke is also a recognised complication of HIV, and therefore would be expected to have showed increased occurrence within PLHIV. It has been estimated that 1% to 5% of HIV-positive patients develop stroke[27]. Our findings also showed an increased pattern of risk for incident stroke, with a hazard ratio of 2.14 (95% CI 1.39-3.30, p=0.0006). Whilst previous research has shown that people from black and minority ethnic (BME) backgrounds are more likely to have risk factors for stroke such as diabetes and high blood pressure[28], ethnicity was not a significant risk factor for the development of stroke in our population.

New cases of type 2 diabetes among people from BME backgrounds have risen with an increase of 26% in black and 23% in Asian and Asian British backgrounds[29]. Whilst, no significant difference in the hazard ratio for incident diabetes was observed between HIV-positive and HIV-negative controls, being of Asian ethnicity was a significant risk factor in

the likelihood of developing diabetes in our cohort. An increase was also observed in people of black ethnicity, however this result was not significant.

End-stage renal disease is a complication of HIV infection, and so would be expected to show an increased prevalence within the PLHIV population[30]. Our findings reflected this increased prevalence in PLHIV in the period prior and post to recorded diagnosis with a reported hazard ratio of incident disease of 1.25 (95% CI 1.02-1.53, p=0.0340).

There was no significant difference between the proportion of PLHIV and control patients having an osteoporosis diagnosis at baseline. However, there was an increased hazard ratio for the development of osteoporosis after HIV diagnosis (HR 3.92; 95% CI 2.38-6.44, p=<0.0001). It is noteworthy that these analyses may have been influenced by the low numbers of patients diagnosed with osteoporosis in both cohorts. Previous studies have demonstrated an increased prevalence of osteoporosis within the HIV-positive population, mainly attributed to the effects of antiretroviral therapy[31].

A limitation of this study was that the coding of HIV was likely to have been underrepresented due to the majority of PLHIV being diagnosed and treated in other settings, such as sexual health/genitourinary medicine (SH/GUM) clinics. Patients diagnosed with HIV in SH services may not have provided consent for their GP to be informed, especially in earlier years analysed, and therefore would not be identifiable in the CPRD database. The increase observed in many of the comorbidities at baseline may be due in part to undiagnosed HIV infection. This study did not account for HIV duration or HIV treatment duration. Hence the increased comorbidities may have been a result of either

longstanding untreated HIV infection or treatment with older antiretroviral therapies. The majority of antiretroviral treatments are dispensed in a secondary care setting, this data is not readily available in the UK and was therefore not included in this analysis.

In conclusion, patients with HIV were at higher risk of developing several comorbidities as well as an increase in HIV-related complications. This highlights the need for PLHIV to have annual reviews to monitor the development of comorbidities in line with the British HIV Association (BHIVA) quality standards for care[32]. An improved awareness of these comorbidities and complications, both by clinicians and patients themselves, will hopefully translate into earlier diagnosis, improved treatment of these conditions and therefore an improved survival and quality of life.

Statements

Table 1: Baseline characteristics

	PLHIV	HIV-negative	p-value
N	2,945	5,890	
Males, n(%)	1,941 (65.9)	3,882 (65.9)	1
Age, mean (SD)	39.1 (12.7)	39.1 (12.7)	1
Age, n(%)			
<18	97 (3.3)	204 (3.5)	<0.0001
18 – 30	576 (19.6)	1,158 (19.7)	
31 – 40	1,048 (35.6)	2,048 (34.8)	
41 – 50	715 (24.3)	1,457 (24.7)	
51 – 60	345 (11.7)	690 (11.7)	
>60	164 (5.6)	333 (5.7)	
BMI kg/m^2, mean (SD)	25.2 (5.4)	27.5 (6.1)	<0.0001
BMI, n(%)			
Underweight (<18.5)	56 (1.9)	22 (0.4)	0.0020
Normal weight (18.5-25)	538 (18.3)	494 (8.4)	
Overweight (25-30)	307 (10.4)	438 (7.4)	
Obese (>30)	173 (5.9)	388 (6.6)	
Missing	1,871 (63.5)	4,548 (77.2)	
Ethnicity, n(%)			<0.0001
White	1,336 (45.4)	3,177 (53.9)	
Black	770 (26.1)	347 (5.9)	
Asian	74 (2.5)	332 (5.6)	
Other	131 (4.4)	173 (2.9)	
Missing	634 (21.5)	1,861 (31.6)	
Prior CNS comorbidities			
Depression	645 (21.9)	949 (16.1)	<0.0001
Anxiety	287 (9.8)	493 (8.4)	0.0350
Sleep disorders	228 (7.7)	271 (4.6)	<0.0001
Prior comorbidities			
Hypertension	219 (7.4)	417 (7.1)	0.5703
Cancer	204 (6.9)	162 (2.8)	<0.0001
Cardiovascular disease	132 (4.5)	129 (2.2)	<0.0001
Diabetes	73 (2.5)	121 (2.1)	0.2277
End-stage renal disease	68 (2.3)	68 (1.2)	<0.0001
Stroke	33 (1.1)	26 (0.4)	0.0004
Osteoporosis	10 (0.3)	20 (0.3)	1.0000

Table 2: Analysis cohort populations

Analysis cohort	PLHIV	HIV-negative
Anxiety	2,254	4,508
Depression	1,670	3,340
Sleep disorder	2,486	4,972
Renal disease	2,820	5,640
Osteoporosis	2,915	5,830
Diabetes	2,764	5,528
CVD	2,711	5,422
Hypertension	2,425	4,850
Stroke	2,887	5,774
Cancer	2,607	5,214

Table 3: Cox proportional hazard model for comorbidities

|	CNS comorbidities			Other comorbidities						
	Anxiety	**Depression**	**Sleep disorder**	**Renal disease**	**Osteoporosis**	**Diabetes**	**CVD**	**Hypertension**	**Stroke**	**Cancer**
Cohort										
HIV-negative	1	1	1	1	1	1	1	1	1	1
PLHIV	1.21 (0.97 – 1.51) P=0.0826	1.66 (1.41 – 1.97) P=<0.0001	1.76 (1.42 – 2.20) P=<0.0001	1.25 (1.02 – 1.53) P=0.0340	3.92 (2.38 – 6.44) P=<0.0001	1.09 (0.84 – 1.43) P=0.5098	1.13 (0.88 – 1.45) P=0.3396	1.05 (0.87 – 1.26) P=0.6310	2.14 (1.39 – 3.30) P=0.0006	1.94 (1.59 – 2.39) P=<0.0001
Gender										
Male	1	1	1	1	1	1	1	1	1	1
Female	1.66 (1.34 – 2.05) P=<0.0001	1.31 (1.10 – 1.56) P=0.0029	1.12 (0.89 – 1.41) P=0.3367	1.59 (1.31 – 1.93) P=<0.0001	3.59 (2.19 – 5.88) P=<0.0001	0.85 (0.65– 1.12) P=0.2502	0.63 (0.48– 0.84) P=0.0013	0.97 (0.81 – 1.17) P=0.7677	0.96 (0.59 – 1.56) P=0.8592	0.95 (0.76 – 1.19) P=0.6490
Age at index	1.00 (0.99 – 1.01) P=0.5939	1.01 (1.01 – 1.02) P=<0.0001	1.01 (1.00 – 1.02) P=0.2021	1.00 (0.99 – 1.00) P=0.4563	1.07 (1.05 – 1.08) P=<0.0001	1.05 (1.04 – 1.06) P=<0.0001	1.06 (1.05 – 1.07) P=<0.0001	1.06 (1.05 – 1.06) P=<0.0001	1.06 (1.04 – 1.08) P=<0.0001	1.06 (1.05 – 1.06) P=<0.0001
Ethnicity										
White	1	1	1	1	1	1	1	1	1	1
Asian	0.38 (0.20 – 0.72) P=0.0031	0.99 (0.69 – 1.42) P=0.9615	0.72 (0.41 – 1.27) P=0.2590	0.41 (0.23 – 0.75) P=0.0041	1.02 (0.31 – 3.32) P=0.9715	2.03 (1.22 – 3.37) P=0.0063	1.77 (1.14 – 2.76) P=0.0116	1.48 (0.99 – 2.22) P=0.0571	0.91 (0.28 – 2.93) P=0.8754	0.68 (0.37 – 1.24) P=0.2080
Black	0.26 (0.17 – 0.41) P=<0.0001	0.53 (0.40 – 0.70) P=<0.0001	0.59 (0.41 – 0.85) P=0.0043	0.29 (0.19 – 0.44) P=<0.0001	0.17 (0.05 – 0.57) P=0.0042	1.23 (0.82 – 1.85) P=0.3195	0.49 (0.28 – 0.84) P=0.0095	1.48 (1.12 – 1.94) P=0.0050	0.68 (0.31 – 1.50) P=<0.0001	0.77 (0.55 – 1.08) P=0.1270
Other	0.70 (0.38 – 1.29) P=0.2506	0.70 (0.42 – 1.11) P=0.1205	1.28 (0.79 – 2.07) P=0.3236	0.68 (0.39 – 1.20) P=0.1828	0.43 (0.06 – 3.13) P=0.4029	1.23 (0.60 – 2.52) P=0.5658	0.52 (0.19 – 1.42) P=0.2032	0.88 (0.50 – 1.53) P=0.6480	0.79 (0.19 – 3.26) P=0.7432	1.03 (0.59 – 1.80) P=0.9200
Missing	0.51 (0.40 – 0.67) P=<0.0001	0.47 (0.38 – 0.58) P=<0.0001	0.53 (0.40 – 0.70) P=<0.0001	0.51 (0.40 – 0.65) P=<0.0001	0.57 (0.29 – 1.09) P=0.0896	0.46 (0.32 – 0.66) P=<0.0001	0.63 (0.47 – 0.84) P=0.0016	0.61 (0.49 – 0.76) P=<0.0001	0.64 (0.36 – 1.14) P=0.1297	0.57 (0.43 – 0.75) P=<0.0001
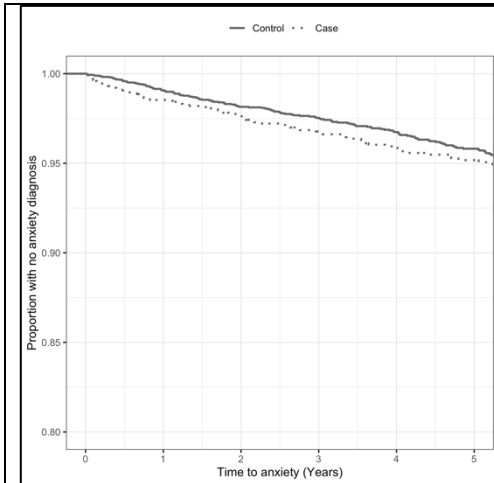
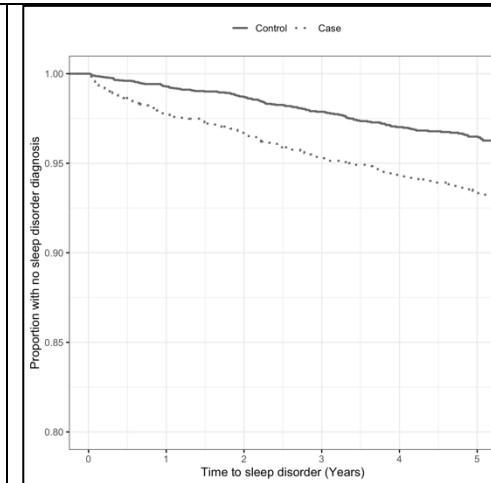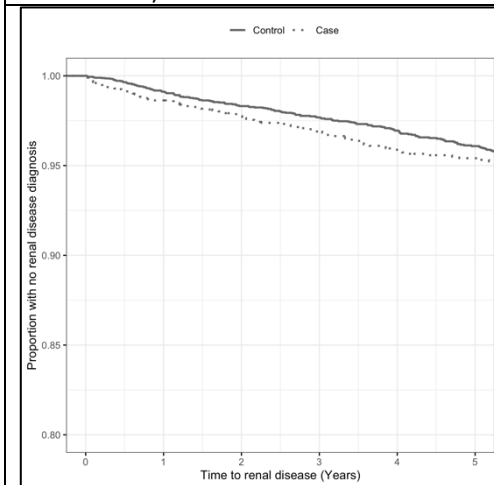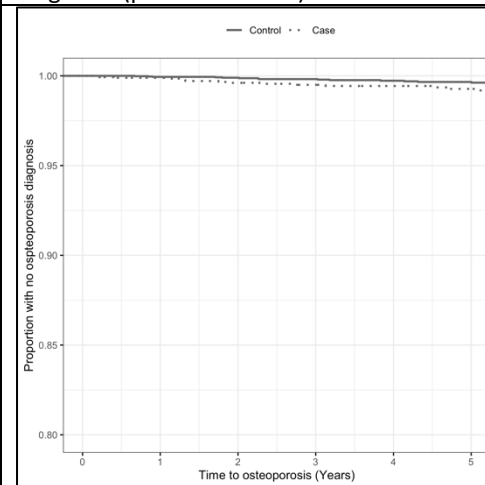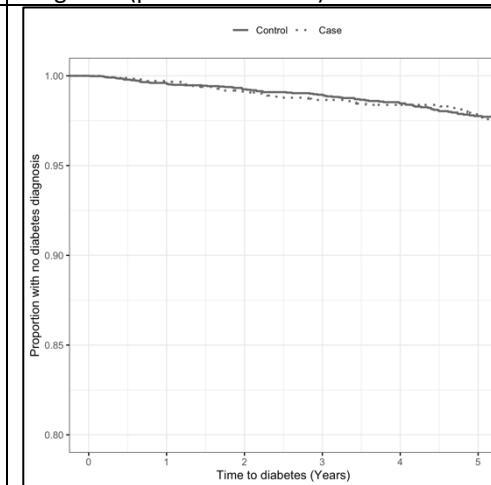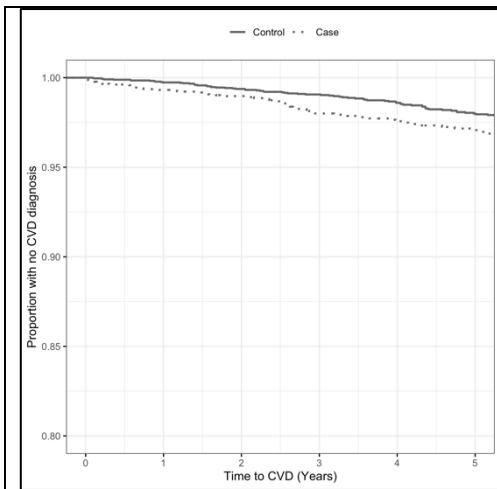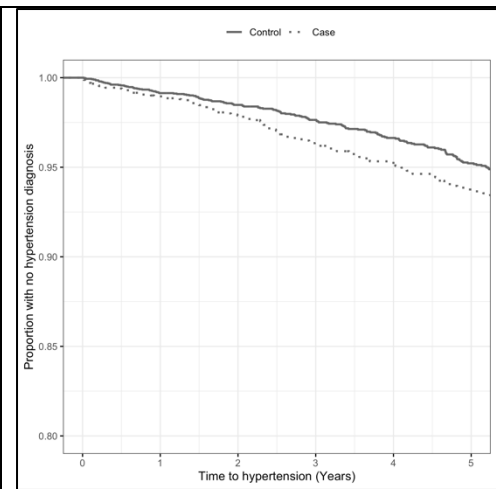|		
Figure 1a| Time to first anxiety diagnosis (p-value=0.200)	Figure 1b | Time to first depression diagnosis (p-value<0.0001)	Figure 1c | Time to first sleep disorder diagnosis (p-value: <0.0001)
Figure 1d | Time to first renal disease diagnosis (p-value: 0.0800)	Figure 1e | Time to first osteoporosis diagnosis (p-value: 0.300)	Figure 1f | Time to first diabetes diagnosis (p-value: 1.000)
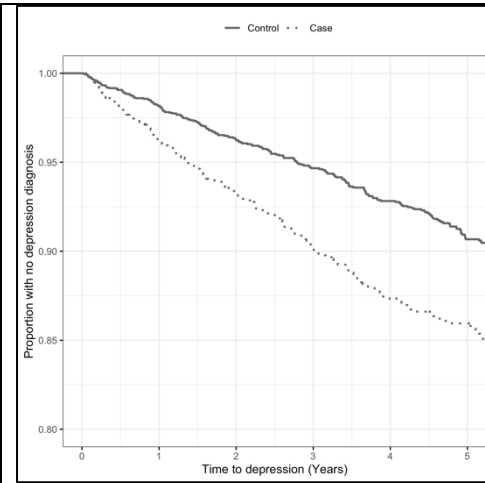
Figure 1g | Time to first CVD diagnosis (p-value: 0.0100)

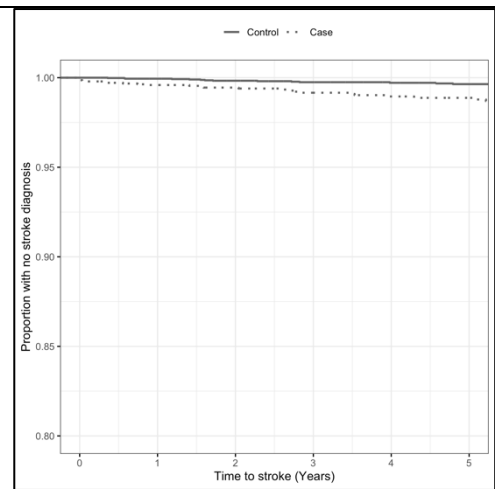Figure 1h | Time to first hypertension diagnosis (p-value: 0.200)

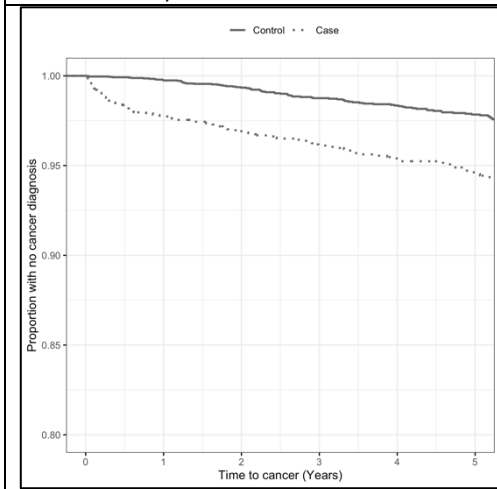Figure 1i | Time to first stroke diagnosis (p-value: <0.0001)

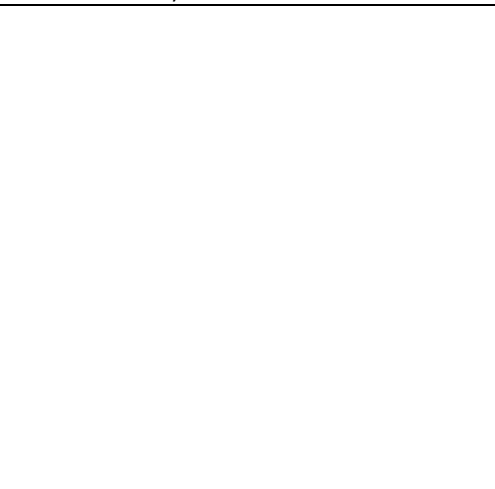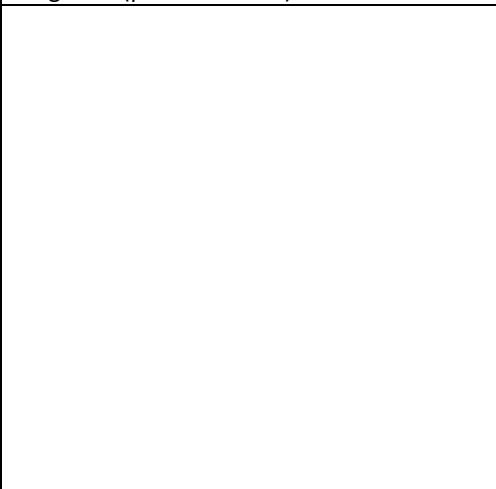Figure 1j | Time to first cancer diagnosis (p-value: <0.0001)

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