Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study

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Summary

Background Whether the reported high risk of age-related diseases in HIV-infected people is caused by biological ageing or HIV-associated risk factors such as chronic immune activation and low-grade inflammation is unknown. We assessed time trends in age-standardised and relative risks of nine serious age-related diseases in a nationwide cohort study of HIV-infected individuals and population controls.

Methods We identified all HIV-infected individuals in the Danish HIV Cohort Study who had received HIV care in Denmark between Jan 1, 1995, and June 1, 2014. Population controls were identified from the Danish Civil Registration System and individually matched in a ratio of nine to one to the HIV-infected individuals for year of birth, sex, and date of study inclusion. Individuals were included in the study if they had a Danish personal identification number, were aged 16 years or older, and were living in Denmark at the time of study inclusion. Data for study outcomes were obtained from the Danish National Hospital Registry and the Danish National Registry of Causes of Death and were cardiovascular diseases (myocardial infarction and stroke), cancers (virus associated, smoking related, and other), severe neurocognitive disease, chronic kidney disease, chronic liver disease, and osteoporotic fractures. We calculated excess and age-standardised incidence rates and adjusted incidence rate ratios of outcomes for time after HIV diagnosis, highly active antiretroviral therapy (ART) initiation, and calendar time. The regression analyses were adjusted for age, sex, calendar time, and origin.

Findings We identified 5897 HIV-infected individuals and 53073 population controls; median age was 36·8 years (IQR 30·6–44·4), and 76% were men in both cohorts. Dependent on disease, the HIV cohort had 55050–57631 person-years of follow-up and the population controls had 638204–659237 person-years of follow-up. Compared with the population controls, people with HIV had high excess and relative risk of all age-related diseases except other cancers. Overall, the age-standardised and relative risks of cardiovascular diseases, cancers, and severe neurocognitive disease did not increase substantially with time after HIV diagnosis or ART initiation. Except for chronic kidney diseases, the age-standardised and relative risks of age-related diseases did not increase with calendar time.

Interpretations Severe age-related diseases are highly prevalent in people with HIV, and continued attention and strategies for risk reduction are needed. The findings from our study do not suggest that accelerated ageing is a major problem in the HIV-infected population.

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Introduction

HIV-infected individuals are at increased risk of several age-related diseases including myocardial infarction,[1] stroke,[2] some non-AIDS associated cancers,[3] severe neurocognitive disease,[4] chronic kidney disease,[5] chronic liver disease,[6] and osteoporotic fractures.[7] Despite the protective effects of highly active antiretroviral therapy (ART), HIV might have a detrimental effect on the risk of these diseases partly as a result of HIV-induced chronic immune activation, persistent low-grade inflammation, and potentially accelerated ageing.[8] Consequently, risks of severe age-related diseases might increase not only with age, but also with duration of HIV and ART, and with later calendar years independent of age.

In this study, we used a nationwide population-based cohort of HIV-infected individuals and a comparison cohort from the general population to estimate time trends in the risk of nine serious age-related diseases that are highly prevalent in people with HIV.

Methods

Study design and participants

As of Jan 1, 2014, Denmark had a population of 5·6 million, with an estimated HIV prevalence of 0·1% in adults. Treatment of HIV is restricted to eight specialised centres, in which patients are seen on an outpatient basis every 12–24 weeks. Health care in Denmark is tax-supported and antiretroviral treatment is provided free of charge. ART is prescribed according to national guidelines.[9]

The primary data source for our study was the Danish HIV Cohort Study (DHCS), which is a nationwide,

Research in context

Evidence before this study
We searched PubMed with the terms ("HIV" and "trends" and "disease" or "co-morbidity" or "age-related disease"), ("HIV" and "co-morbidity" or "age-related disease" or "cause of death"), and ("HIV" and "accelerated aging") to identify original research reports published in English after Jan 1, 2000, of the investigation of age-standardised trends in risk of age-related diseases over calendar time, time of HIV infection and exposure to highly active antiretroviral treatment in HIV-infected individuals. These individuals are at a greater risk than are the general population of several age-related diseases. HIV-induced chronic immune activation, persistent low-grade inflammation, and potentially accelerated biological ageing have been suggested to have a detrimental effect on the risk of age-related diseases such as cardiovascular disease, non-AIDS cancer, severe neurocognitive disease, chronic kidney and liver diseases, and osteoporosis. Although, the risks of some age-related diseases might be similar to risks in the general population, the risks of severe age-related diseases might increase with duration of HIV and antiretroviral treatment.

Added value of this study
Our findings did not lend support to a larger cumulative effect of time after HIV diagnosis or antiretroviral treatment on absolute or relative risks of major age-related diseases, hence arguing against accelerated ageing as a major problem in the HIV-infected population. Furthermore, our results do not indicate that the risks of most age-related diseases in the HIV-infected population increase with calendar time.

Implications of all the available evidence
These results are of interest to physicians treating HIV-infected individuals and could potentially diminish the fear induced in the HIV-infected population from focus on premature ageing.

prospective, population-based cohort study of all HIV-infected Danish individuals treated at Danish hospitals since Jan 1, 1995. DHCS has been described in detail elsewhere.[9]

We used the unique ten-digit personal identification number assigned to all individuals in Denmark at birth or on immigration to track individuals in the Danish Civil Registration System (DCRS), Danish National Hospital Registry (DNHR), and Danish National Registry of Causes of Death (DNRCD,[9] and further described in the appendix p 1). The study period was from Jan 1, 1995, until June 1, 2014.

From DHCS, we identified all HIV-infected individuals who had a Danish personal identification number, were 16 years or older, were living in Denmark at the date of study inclusion, and were attending HIV care in Denmark between Jan 1, 1995, and June 1, 2014. Individuals diagnosed with age-related diseases (except osteoporotic fractures) before inclusion in the study were excluded.

The comparison cohort consisted of nine controls matched with each HIV-infected individual for year of birth, sex, and date of inclusion in the study. The criteria for inclusion and exclusion were the same as for the HIV-infected cohort with the exception of HIV infection.

Data were obtained from DNHR, DNRCD, and DCRS with approval from the Danish National Board of Health. The study was approved by the Danish Data Protection Agency (journal number 2008-41-1781). Ethics approval and individual consent are not required by Danish legislation governing this type of research on HIV-infected individuals.

Outcomes
The study outcome was time to age-related diseases defined as the first date an individual was registered in the hospital or death registries with the following diagnoses: myocardial infarction, stroke, cancer, severe neurocognitive disease, chronic kidney disease, chronic liver disease, and osteoporotic fractures. In agreement with previously applied methods by the DHCS,[3] we distinguished between cancers associated with oncogenic virus and smoking-related and other cancers. Definitions and diagnostic codes are presented in the appendix pp 2–3.

Data were recorded for the following covariates: age (time-updated variable, included as a continuous variable, second, third, or fourth order, or squared when appropriate), sex, calendar years (time-updated for 1995–99, 2000–03, 2004–07, 2008–11, and 2012–14), and origin (Danish vs non-Danish).

Statistical analysis
To illustrate the demographic changes of DHCS, we computed follow-up from study inclusion (the most recent of Jan 1, 1995, date of HIV diagnosis, or date of immigration) to the first of date of death, emigration, loss to follow-up, or June 1, 2014. For each individual, we calculated age at Jan 1 in each new calendar year, or at the date of entry into the cohort in that specific calendar year. We calculated the proportion of HIV-infected individuals who attended HIV care in a particular calendar year (1995 to 2014) by age group (≤40 years, 40–49 years, 50–59 years, 60–69 years, and ≥70 years).

To assess the risk of age-related diseases, we computed follow-up from study inclusion (as defined above) until date of incident age-related disease, death, emigration, loss to follow-up, or June 1, 2014, whichever occurred first. We calculated crude incidence rates per 1000 person-years of follow-up (absolute risk) and excess incidence rate (excess risk), and used Poisson regression analysis to calculate crude and adjusted incidence rate ratios (aIRR; relative risk) for HIV-infected individuals

versus controls and 95% CIs. Analyses were adjusted for the covariates (age, sex, calendar year, and origin). Our model was based on the minimum set of explanatory variables needed to estimate time trends unaffected by confounders. The choice of variables was guided by clinical knowledge. All variables were forced into the model independent of significance. We also calculated crude incidence rate and aIRR according to age groups (16–44 years, 45–54 years, 55–64 years, and ≥65 years).

To assess trends in absolute risk with time after HIV diagnosis, ART initiation, and calendar time, we used the direct standardisation method with an internal population as a standard to calculate standardised incidence rates. To ensure a representative standardisation, we used the age and sex distributions in years 10–12 after HIV diagnosis, years 10–15 after ART initiation, and the calendar years 2012–14 as standard. To assess trends in relative risk with time after HIV diagnosis and after ART initiation, and with calendar time, we calculated aIRR (HIV-infected individuals vs controls) for all age-related diseases.

SPSS (version 15.0), Stata (version 11.1), and R software (version 2.11.1) were used for data analysis.

Role of the funding source

The funder was not involved in study design, data gathering, analysis, or interpretation, report writing, or decision to submit the paper. The authors had full access to all data in the study and the responsibility for the decision to submit for publication was shared between all authors.

Results

6174 HIV-infected individuals met inclusion criteria; the proportion older than 50 years increased from 13% (276 of 2202) in 1995 to 43% (1791 of 4190) in 2014 (figure 1). 277 HIV-infected individuals were excluded because of a diagnosis of age-related disease before the date of inclusion, leaving 5897 HIV-infected individuals and 53073 controls in the study. The median age of the HIV-infected individuals and control cohorts was 36·8 years and 76% were men (table).

Depending on the disease under observation, HIV-infected individuals had 55050–57631 person-years of follow-up and control individuals had 638204–659237 person-years of follow-up (table). In total, 24 (0·4%) of 5897 HIV-infected individuals and 58 (0·1%) of 53073 controls were registered as lost to follow-up. Apart from other cancers, HIV-infected individuals had a higher excess and relative risk of all age-related diseases than did the controls (appendix p 4).

For all age-related diseases the absolute risks increased with increasing age in HIV-infected individuals (figure 2). However, with the exception of osteoporotic fractures, relative risks for people with HIV compared with controls decreased.

Age-standardised risk of cardiovascular diseases, cancers, severe neurocognitive disease, or chronic kidney
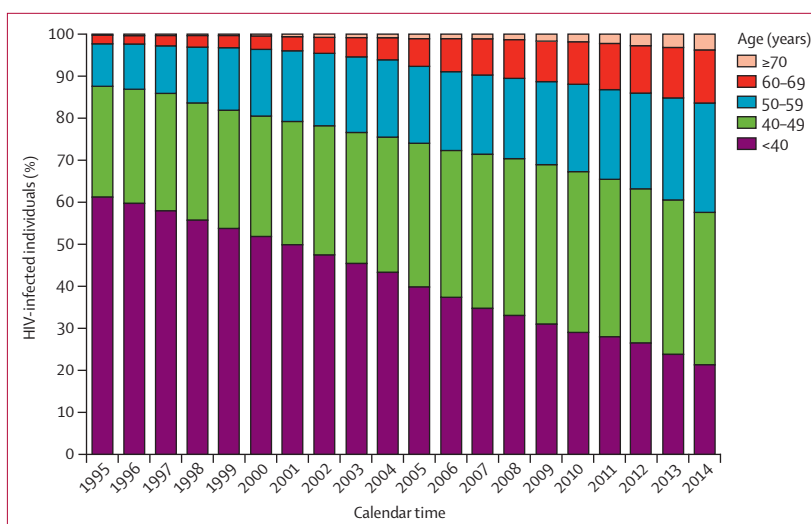

Figure 1: Changes in age with calendar time for the Danish HIV Cohort Study

	HIV-infected individuals	Control cohort
Individuals	5897	53073
Sex, male	4469 (76%)	40221 (76%)
Age (years)	36·8 (30·6–44·4)	36·8 (30·6–44·4)
Danish born	4085 (69%)	47987 (90%)
Route of transmission		
Men who have sex with men	2733 (46%)	..
Injection drug use	587 (10%)	..
Heterosexual	2204 (37%)	..
Other	373 (6%)	..
Hepatitis C	881 (15%)	..
HIV before 1995	1937 (33%)	..
AIDS	476 (8%)	..
ART	243 (4%)	..
CD4 count (cells per µL)	300* (124–490)	..
Viral load <400 copies per mL	669† (12%)	..
Total observation time (person-years)	55050–57631	638204–659237
Myocardial infarctions	170 (3%)	1068 (2%)
Stroke	222 (4%)	1563 (3%)
Chronic kidney diseases	115 (2%)	348 (0·7%)
Chronic liver diseases	127 (2%)	386 (0·7%)
Severe neurocognitive diseases	89 (2%)	202 (0·4%)
Osteoporotic fractures	457 (8%)	2967 (6%)
Virus-associated cancers	273 (5%)	259 (0·5%)
Smoking-associated cancers	105 (2%)	727 (1%)
Other cancers	175 (3%)	1925 (4%)

Data are number, number (%), or median (IQR). ART=antiretroviral therapy. *Data missing for 68 individuals. †Data missing for 440 individuals.

Table: Baseline characteristics of the study population

disease did not increase substantially with time after HIV diagnosis (figure 3). However, the age-standardised risk of chronic liver disease and osteoporotic fractures seemed to increase with time after HIV diagnosis
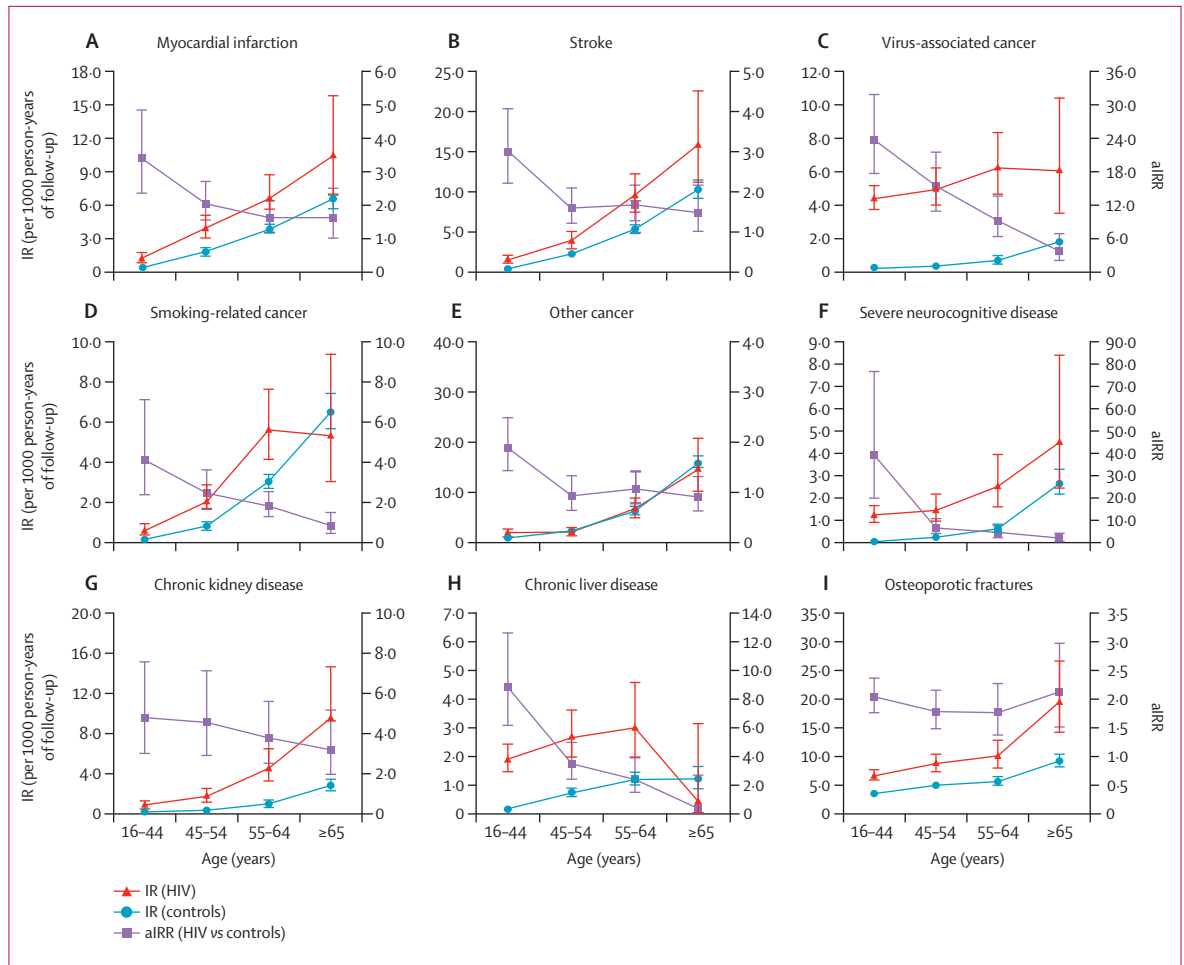
***Figure 2:* Absolute risk and relative risk of serious age-related diseases with age in HIV-infected individuals and controls**
Vertical lines are the 95% CIs. IR=incidence rate. aIRR=adjusted incidence rate ratio (adjusted for sex, calendar year [time-updated for 1995–99, 2000–03, 2004–07, 2008–11, and 2012–14], and Danish or non-Danish origin).

(figure 3). With the exception of chronic liver disease and osteoporotic fractures, the relative risks of the age-related diseases were stable or decreased with time after HIV diagnosis compared with the control cohort (figure 4).

The trends in age-standardised and relative risk of age-related diseases with time after ART initiation were almost identical to the time after HIV diagnosis except for increased age-standardised risk of chronic kidney disease and a stable age-standardised risk of chronic liver disease (appendix pp 5–6).

With the exception of chronic kidney disease, we noted an overall stable or decreasing trend in age-standardised and relative risks in the other age-related diseases with calendar time in the HIV-infected individuals (figures 5 and 6); the age-standardised risk of chronic kidney disease increased after 1995–99 and a similar trend was noted in the control cohort (figure 5). For several age-related diseases (myocardial infarction, stroke, smoking-related cancer, and osteoporotic fractures) the age-standardised risks decreased overall

with calendar time in both cohorts, while the risks of virus-associated cancer and severe neurocognitive disease decreased substantially in the HIV-infected population independently of the risks in the background population (figure 5). The relative risks decreased for all diseases with calendar time (figure 6). For comparison, the non-standardised incidence rates are shown in the appendix pp 7–8.

Discussion
In this study, we noted that age-standardised and relative risks of cardiovascular diseases, cancers, and severe neurocognitive disease in Danish HIV-infected individuals did not increase with time after HIV diagnosis or ART initiation. Although the age-standardised risk of chronic kidney disease increased with time after ART initiation, no substantial increase was noted with time after HIV diagnosis. The opposite was noted for risk of chronic liver disease, whereas the age-standardised and relative risks of osteoporotic
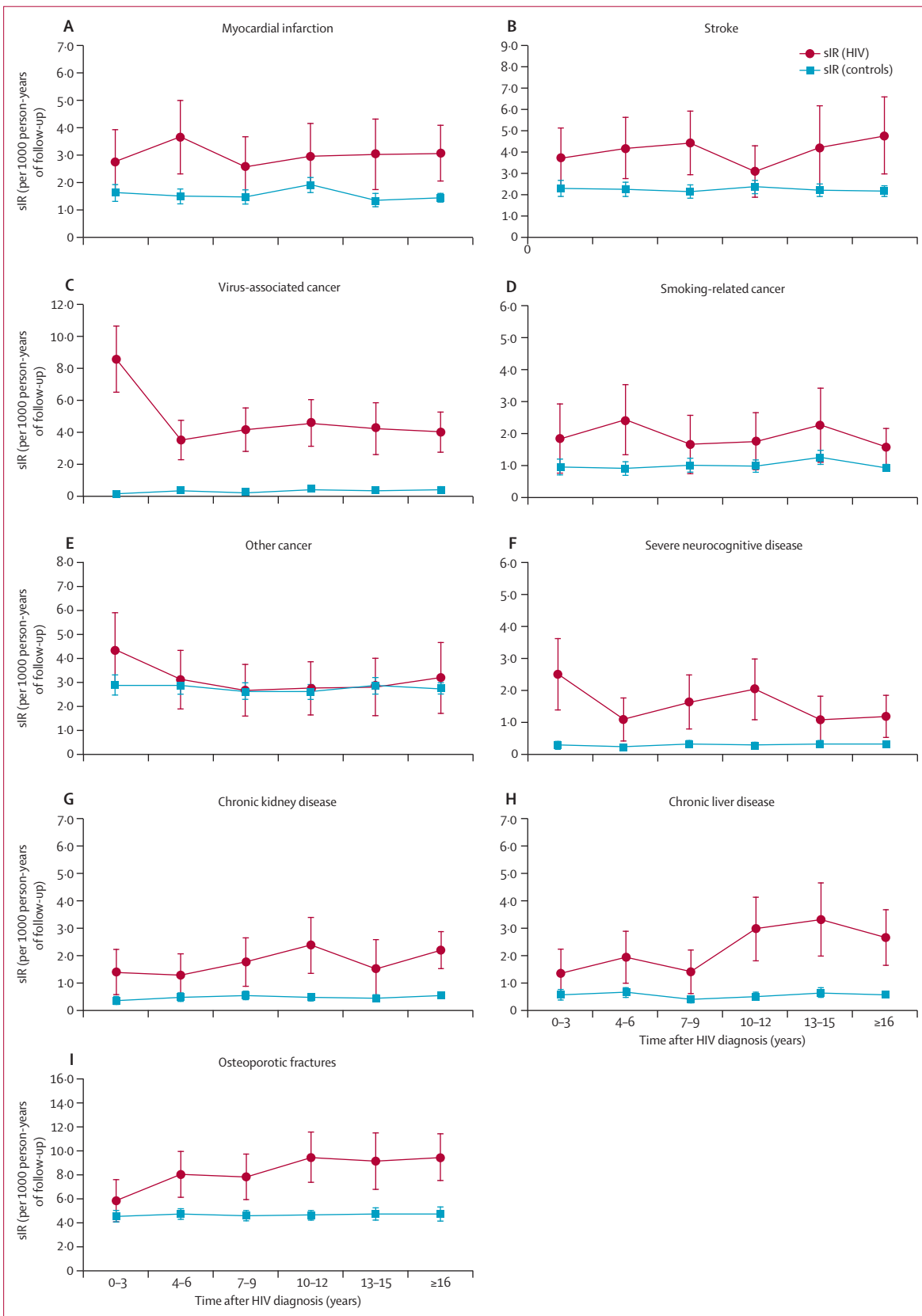
Figure 3: **Absolute risk (age-standardised) of serious age-related diseases with time after HIV diagnosis** Standardised incidence rate (sIR; standardised for age and sex distribution in person-years of follow-up during 10–12 years after HIV transmission).
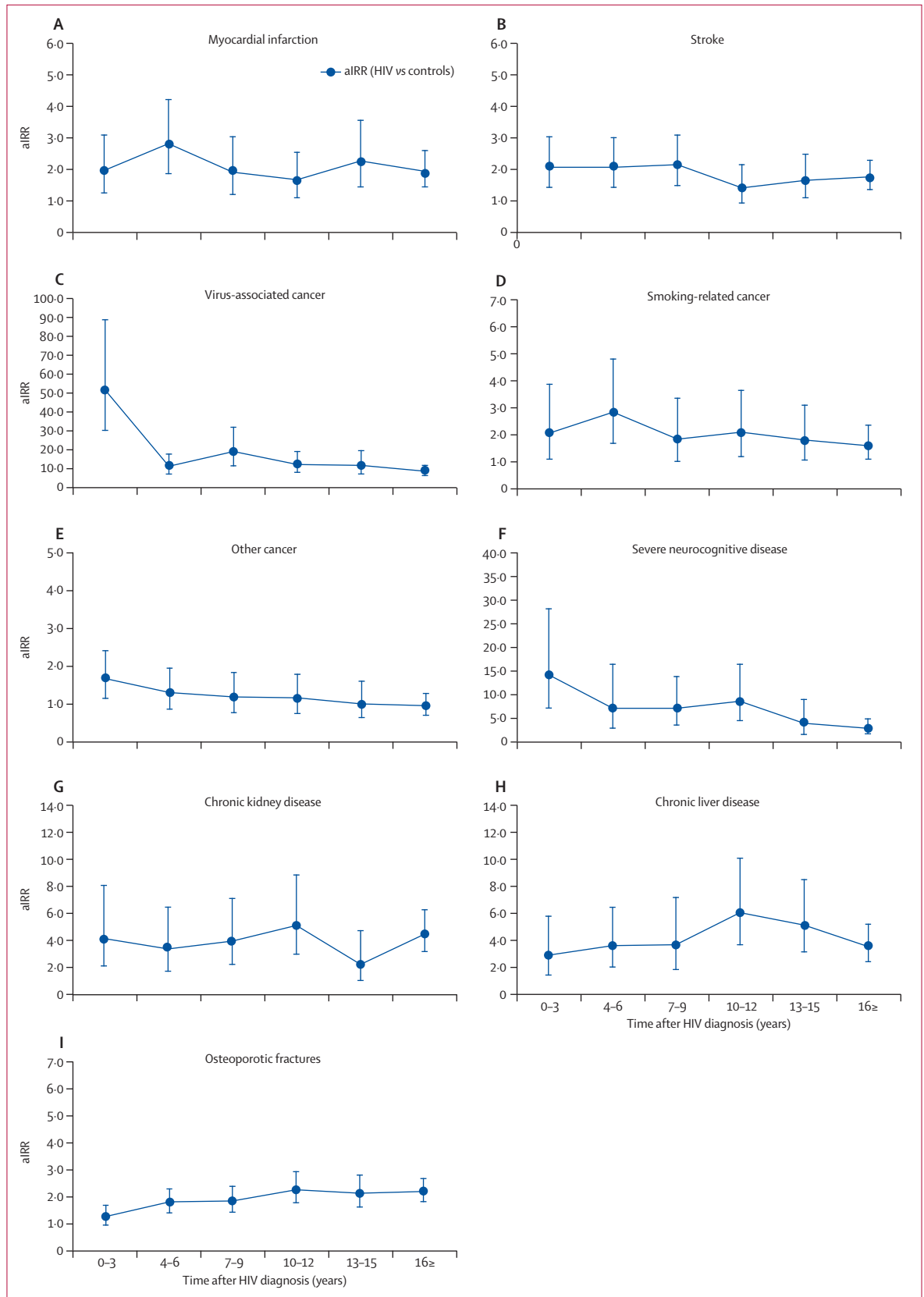
Figure 4: Relative risk of serious age-related diseases with time after HIV diagnosis
aIRR=adjusted incidence rate ratio (adjusted for sex, age [time-updated for 30–34 years, 35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, and ≥65 years], calendar years [time-updated for 1995–99, 2000–03, 2004–07, 2008–11, and 2012–14], and Danish or non-Danish origin). Vertical lines are the 95% CIs.
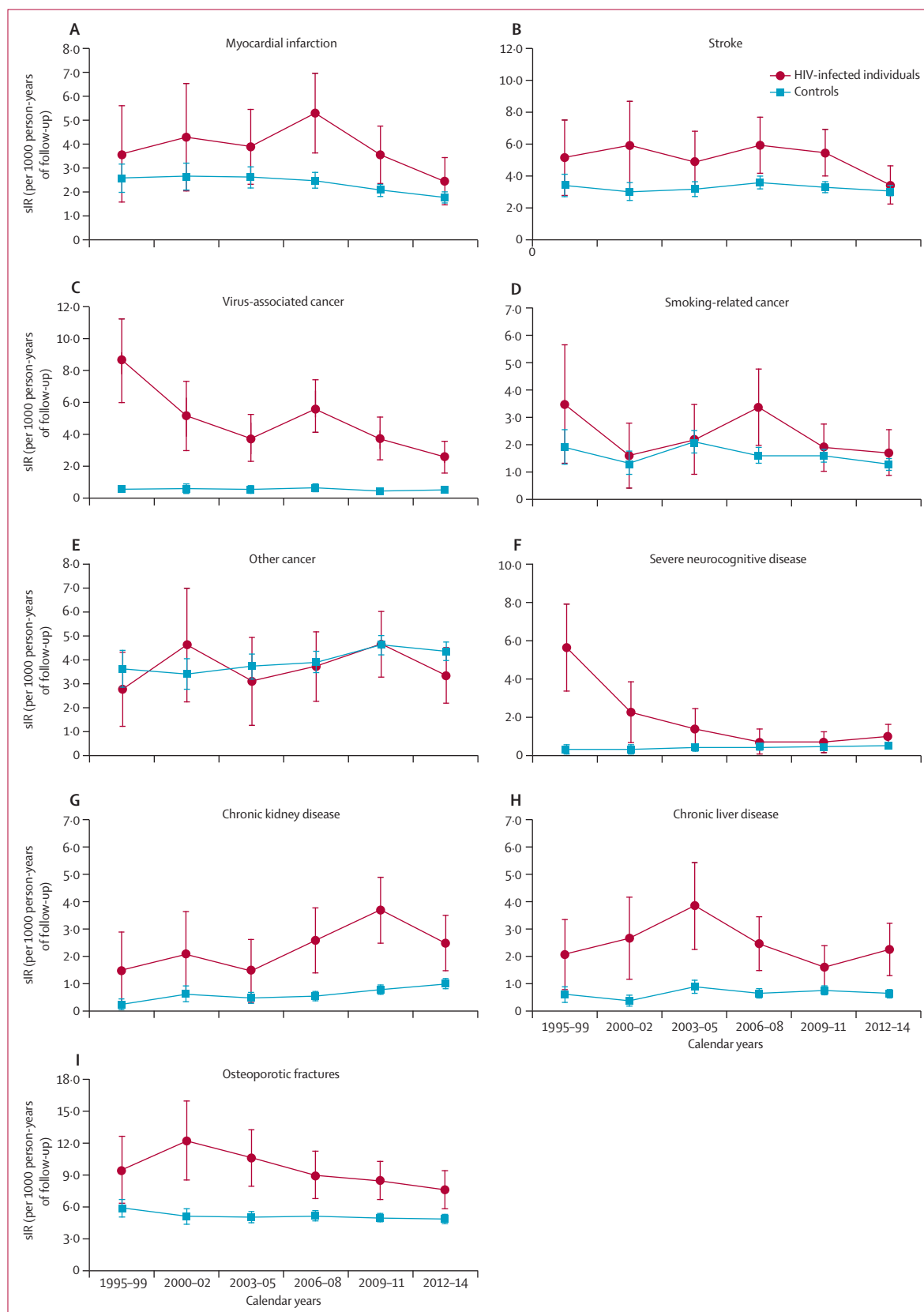
Figure 5: **Absolute risk (age-standardised) of serious age-related diseases with calendar time**
sIR=standardised incidence rate (standardised for age and sex distribution per person-years of follow-up for 2012–14).
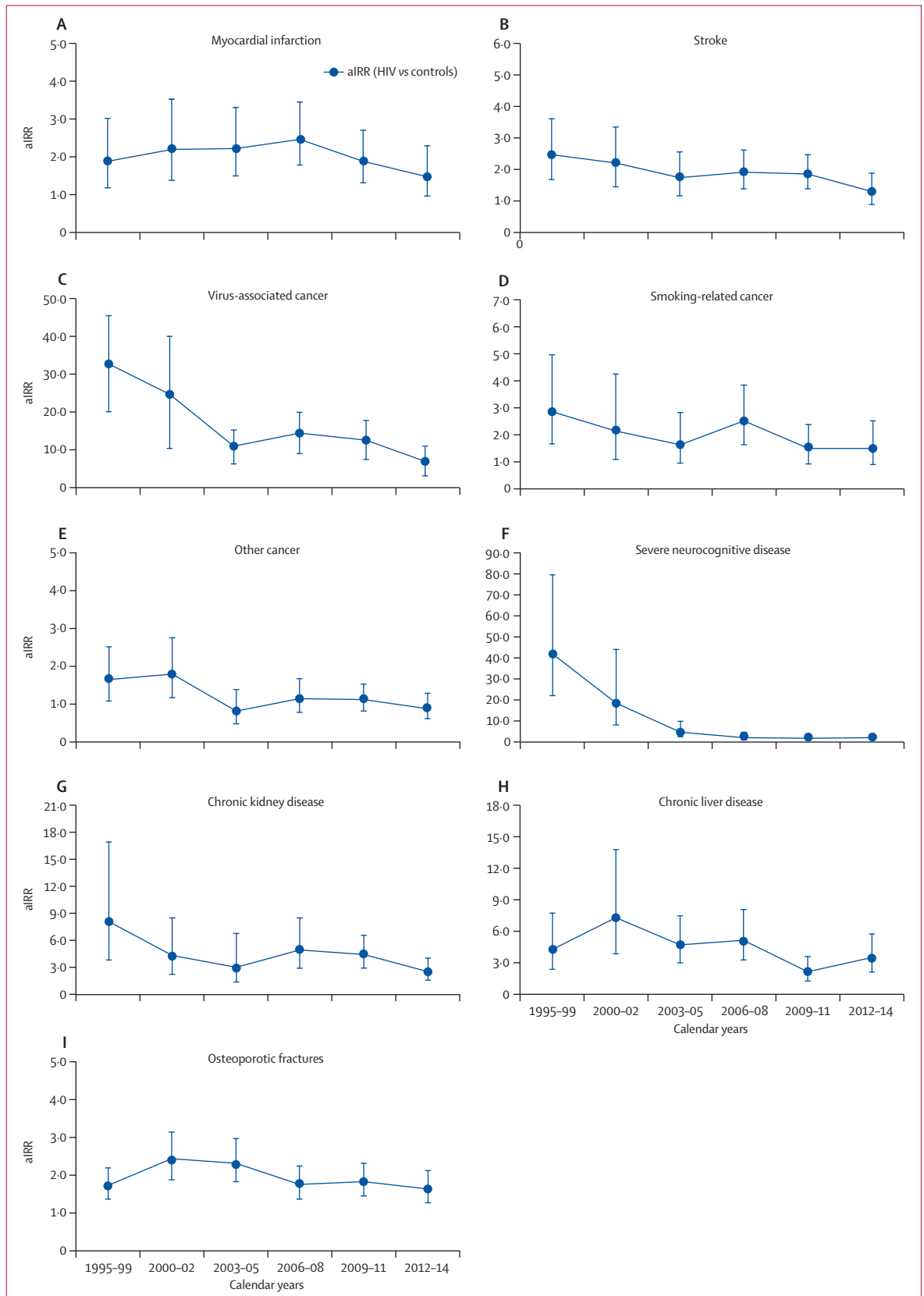
Figure 6: Relative risk of serious age-related diseases with calendar years

aIRR=adjusted incidence rate ratio (adjusted for sex, age [time-updated for 16–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, and ≥65 years], calendar years [time-updated for 1995–99, 2000–03, 2004–07, 2008–11, and 2012–14], and Danish or non-Danish origin). Vertical lines are the 95% CIs.

fractures increased with time after both HIV diagnosis and ART initiation. Except for chronic kidney disease, the age-standardised risk of all age-related diseases decreased with calendar years.

Age was associated with increased absolute risk and reduced relative risk of all major age-related diseases except osteoporotic fractures. These trends indicate that in the younger age groups a small increase in absolute risk of age-related diseases in HIV-infected individuals results in a large increase in relative risk due to the low risk of these diseases in the young background population. HIV-infected users of injectable drugs are prone to infection with hepatitis C virus (HCV) and hence are at risk of severe chronic liver disease. Since injection drug users and HCV are potentially under-represented in the older age groups[10] due to premature death, this could explain the low absolute risk of chronic liver disease in the oldest age group.

Despite ART, HIV-infected individuals are presumed to be affected by chronic immune activation and sustained low-level inflammation,[11] which is assumed to be associated with increased frailty, early ageing, and risk of serious age-related diseases, especially cardiovascular diseases.[12] We cannot rule out that inflammation might explain some of the excess risk of age-related diseases in HIV-infected individuals. Nevertheless, we noted a stable or slightly reduced age-standardised and relative risk of cardiovascular diseases, cancers, and severe neuro-cognitive disease with time after HIV diagnosis and ART initiation. This finding indicates that in the ART era the cumulative effect of HIV-induced chronic inflammation on risk of age-related diseases is small and does not lend support to the notion that accelerated ageing is a major problem in HIV-infected individuals.

Trends in risk of age-related diseases over calendar time might indicate changes in use of antiretroviral drugs, preventive strategies, and cumulative effects of exposure to HIV or ART. For all diseases except chronic kidney disease, we noted that the age-standardised risk of comorbid diseases remained stable or decreased in the HIV-infected population over recent calendar years. These results are consistent with the greater than 65% reduction in death from cardiovascular diseases, 50% reduction in liver-related death, and stable mortality from non-AIDS-related cancers during 1999–2011 in the D:A:D study.[13]

Structured treatment interruptions have never been used in Denmark. The decline in the risk of cardiovascular diseases after 2006–08 cannot be explained by changes in ART strategies as per the results of the SMART study.[14] We cannot exclude that the use of less toxic ART regimens and regimens that did not include abacavir in high-risk individuals after 2008 might have reduced the risk of cardiovascular diseases. A similar trend, although less pronounced, was noted in the general population, indicating that preventive strategies such as smoking cessation and the use of lipid-lowering and antihypertensive drugs are more likely explanations of the reduced risk. Furthermore, in agreement with the results reported by Klein and colleagues,[15,16] the relative risks of myocardial infarction and stroke in people with HIV in recent years became similar to those in the general population, thus emphasising the potential effect of enhanced attention to and implementation of risk reduction measures for cardiovascular diseases in the HIV-infected population.

Smoking has potentially larger health implications for the HIV-infected population,[3,17–19] than for the general population.[18,19] However, we did not note an increase in the risk of smoking-related cancer with time after HIV diagnosis, ART initiation, or calendar time.

According to the results of ART-CC,[20] the risk of death from non-AIDS malignant diseases increased with time on ART. However, we noted an overall stable age-standardised risk of other cancers with time after HIV diagnosis, ART initiation, and calendar time that was similar to risks of non-AIDS cancers or related death in other studies.[13,21] Importantly, we noted almost equivalent risks of other cancers in the HIV-infected and general populations, indicating no or only minor association between risk of other cancers and HIV infection.

In accordance with the results of earlier studies,[22] we noted a substantial reduction in severe neurocognitive disease over calendar time, which was due to reduced incidence of AIDS dementia complex after the intro-duction of ART. Of interest, severe neurocognitive disease did not increase over time after HIV diagnosis, time after ART initiation, or calendar time, which argues against accelerated ageing leading to increased risk of severe neurocognitive disease.

Abraham and colleagues[23] reported a reduction in risk of end-stage renal disease in the HIV-infected population during 2000–09. These findings are different from our results, and perhaps because of differences in outcome definitions, racial disparities, and prevalence of risk factors. Although the relative risk of chronic kidney disease was not substantially increased with time after HIV diagnosis, the age-standardised risk of chronic kidney disease increased with time after ART initiation. However, our data do not allow us to distinguish between cumulative effects of HIV infection and ART exposure. Furthermore, age-standardised risk of chronic kidney disease increased after 1995–99 in the HIV-infected population. We cannot exclude, that this increase was induced by the use of nephrotoxic antiretroviral drugs during later years. However, in accordance with previous findings for the general population,[24] the risk of chronic kidney disease increased similarly in the control population.

For individuals co-infected with hepatitis B virus (HBV) or HCV, the duration of these infections was colinear with HIV duration and might explain why the risk of chronic liver disease increased with time after HIV diagnosis. The studies of long-term effects of ART on risk of liver disease

are conflicting.[6,25] Although age-standardised and relative risks were stable with time after ART, our data do not allow us to completely distinguish between cumulative effects of HIV infection or ART exposure. The age-standardised risk of chronic liver disease declined substantially during recent years to a level equivalent to that during 1995–99. This trend is consistent with the reduction in risk of liver-related death in the D:A:D study (1999–2011),[13] and might be a result of the reduced risk of HIV infection transmitted through injection drug use, potentially effective treatment of HBV (and HCV), and increased use of less hepatotoxic drugs in later years.

In our study, age-standardised risk of osteoporotic fractures increased with time after HIV diagnosis. Bruera and colleagues' report[26] found an association of reduced bone mineral density with time after HIV diagnosis. The results of randomised controlled trials[27] have shown that bone mineral density seems to decline in HIV-infected individuals in the first 6–12 months after ART initiation (independent of regimen) and then stabilises. However, Bonjoch and co-workers[28] showed that the duration of exposure to protease inhibitors and tenofovir was associated with loss of bone mineral density. Although, age-standardised risk also increased with time after ART, we cannot separate any potential effects of risk factors that might be colinear. Therefore, a cumulative effect of some antiretroviral drugs or an effect of chronic inflammation and sustained immune activation on risk of osteoporotic fractures cannot be excluded.[29] Overall, the age-standardised risk declined substantially with calendar time. Low CD4 cell count, presence of AIDS-defining illness, and low body-mass index[7] are risk factors for osteoporotic fractures, but the reduced risk of fractures over time might be explained by the early initiation of ART, use of less toxic drugs, and increased screening and prophylactic treatment.

The strengths of our study include the use of a population-based, nationwide HIV cohort and a well matched population-based comparison cohort, both with almost complete follow-up. Danish registries provided full access to high-quality data for vital status, hospital contacts, and deaths for all individuals in the study. The high coverage and long follow-up of the Danish HIV-infected population allowed us to assess longitudinal effects of age, calendar time, and time after HIV diagnosis and ART initiation. We used standardised rates to assess time trends in absolute risk to avoid confounding by age. Importantly, access to data for a reliable comparison cohort enabled us to distinguish trends associated with HIV from those occurring in the general population. We are not aware of other studies with a similar design.

Our study has some limitations. Although, we mainly used known codes and definitions for the diseases under observation,[1–4,7,30] the comorbid diseases were identified from hospital registry-based discharge diagnoses and hence there was a risk of misclassification.

We used the same data sources to ascertain the diagnoses for both cohorts and assumed that the accuracy of the data did not vary by HIV status, which minimised differential misclassification. Moreover, any misclassification was unlikely to be associated with the timelines. Our study did not include individuals who were diagnosed with one of the age-related diseases (except osteoporotic fractures) before the date of inclusion in the study; hence, a healthy survivor effect might have been introduced. However, we believe that this does not lead to major bias because only 277 individuals were excluded due to this design. We cannot exclude competing risk by death. Because HIV-infected individuals are monitored at regular visits, risk of surveillance bias and thus earlier diagnosis of age-related diseases cannot be excluded. However, the serious age-related diseases included in the study are unlikely to be substantially under-reported in Danish hospital databases. HIV-infected individuals differ from non-HIV-infected individuals in terms of several variables that might affect the overall risk of age-related diseases. Nevertheless, our aim was not to compare risks in the HIV-infected versus the background populations, but to estimate trends in the relative risk over time. Hence, we included explanatory variables in the regression analyses that could confound the time trends. Nevertheless, we cannot assure inference of the results for every subgroup of HIV-infected individuals.

We conclude that the age-standardised risks of cardiovascular diseases, cancers, and severe neuro-cognitive disease do not seem to increase with time after HIV diagnosis or ART initiation. Since the risk of major age-related diseases (except chronic kidney disease) has declined in recent calendar years, HIV-infected individuals can be assured that their overall risk of major age-related diseases does not seem to increase independently of age. Also our data indicate that in the ART era, the duration of HIV-induced chronic immune activation and sustained inflammation after initiation of ART do not substantially increase the risk of cardiovascular diseases, cancers, or severe neurocognitive disease.

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