Check for updates

Circulation

ORIGINAL RESEARCH ARTICLE

Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV

Systematic Review and Meta-Analysis

Editorial, see p 1113

Anoop S.V. Shah, MD, MPH, PhD
Dominik Stelzle, MD
Kuan Ken Lee, MD
Eduard J. Beck, MD, PhD, FFPH
Shirjel Alam, MD
Sarah Clifford, MD
Chris T. Longenecker, MD
Fiona Strachan, PhD
Shashwatee Bagchi, MD
William Whiteley, MD
Sanjay Rajagopalan, MD
Shyamasundaran Kottilil, MD
Harish Nair, PhD
David E. Newby, MD, PhD
David A. McAllister, MD
Nicholas L. Mills, MD, PhD

BACKGROUND: With advances in antiretroviral therapy, most deaths in people with HIV are now attributable to noncommunicable illnesses, especially cardiovascular disease. We determine the association between HIV and cardiovascular disease, and estimate the national, regional, and global burden of cardiovascular disease attributable to HIV.

METHODS: We conducted a systematic review across 5 databases from inception to August 2016 for longitudinal studies of cardiovascular disease in HIV infection. A random-effects meta-analysis across 80 studies was used to derive the pooled rate and risk of cardiovascular disease in people living with HIV. We then estimated the temporal changes in the population-attributable fraction and disability-adjusted life-years (DALYs) from HIV-associated cardiovascular disease from 1990 to 2015 at a regional and global level. National cardiovascular DALYs associated with HIV for 2015 were derived for 154 of the 193 United Nations member states. The main outcome measure was the pooled estimate of the rate and risk of cardiovascular disease in people living with HIV and the national, regional, and global estimates of DALYs from cardiovascular disease associated with HIV.

RESULTS: In 793 635 people living with HIV and a total follow-up of 3.5 million person-years, the crude rate of cardiovascular disease was 61.8 (95% CI, 45.8–83.4) per 10 000 person-years. In comparison with individuals without HIV, the risk ratio for cardiovascular disease was 2.16 (95% CI, 1.68–2.77). Over the past 26 years, the global population–attributable fraction from cardiovascular disease attributable to HIV increased from 0.36% (95% CI, 0.21%–0.56%) to 0.92% (95% CI, 0.55%–1.41%), and DALYs increased from 0.74 (95% CI, 0.44–1.16) to 2.57 (95% CI, 1.53–3.92) million. There was marked regional variation with most DALYs lost in sub-Saharan Africa (0.87 million, 95% CI, 0.43–1.70) and the Asia Pacific (0.39 million, 95% CI, 0.23–0.62) regions. The highest population-attributable fraction and burden were observed in Swaziland, Botswana, and Lesotho.

CONCLUSIONS: People living with HIV are twice as likely to develop cardiovascular disease. The global burden of HIV-associated cardiovascular disease has tripled over the past 2 decades and is now responsible for 2.6 million DALYs per annum with the greatest impact in sub-Saharan Africa and the Asia Pacific regions.

CLINICAL TRIAL REGISTRATION: URL: https://www.crd.york.ac.uk/prospero. Unique identifier: CRD42016048257.

Key Words: cardiovascular diseases ■ global burden of disease ■ HIV ■ myocardial infarction ■ stroke

Sources of Funding, see page 1109

© 2018 The Authors. *Circulation* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited.

https://www.ahajournals.org/journal/circ

Downloaded from http://ahajournals.org by on June 17, 2024

Clinical Perspective

What Is New?

- Recent studies have identified plausible biological mechanisms, including endothelial dysfunction and arterial inflammation, to explain the association between HIV infection and atherosclerotic disease.
- This article represents a systematic analysis to evaluate the association between HIV and cardiovascular disease and estimate the burden of HIV-associated cardiovascular disease at a national, regional, and global level.
- We report that the risk of cardiovascular disease is increased 2-fold in people living with HIV, and the global burden of HIV-associated cardiovascular disease has tripled over the past 2 decades with the majority of the burden experienced in sub-Saharan Africa and the Asia Pacific region.

What Are the Clinical Implications?

- The combined burden of HIV and cardiovascular disease, especially in high-prevalence regions, has important implications with respect to regional health policies, guidelines, and resource allocation.
- Risk stratification and identification of patients at risk of future cardiovascular disease are already challenging in these regions.
- Whether patients living with HIV should be considered high-risk and appropriate primary prevention pharmacotherapy such as statin therapy should be implemented remains unclear.
- Our estimates have important policy implications for implementing appropriate cardiovascular risk stratification and treatment strategies across healthcare systems, especially in low- and middle-income nations where both HIV and cardiovascular disease remain highly prevalent.

Currently, >35 million people are infected with HIV, with two-thirds being resident in sub-Saharan Africa.[1] Although the global incidence for HIV has stabilized, the provision and widespread distribution of combined antiretroviral therapy[2] has dramatically improved survival with the prevalence of HIV steadily increasing over the past 2 decades.[3] This improvement in survival has been primarily attributed to a reduction in opportunistic infections, especially in the low- and middle-income nations.[1,4] Indeed, most deaths now arise from noncommunicable illnesses, especially cardiovascular disease.[5–7]

Cardiovascular disease is the leading cause of morbidity and mortality worldwide.[8,9] The past 2 decades have seen a substantial increase in the morbidity attributable to cardiovascular disease, with a significant proportion of the burden borne by low- and middle-income nations.[10,11] The highest prevalence rates of HIV have been observed in sub-Saharan Africa. This region has also seen a steady increase in the burden of cardiovascular disease over the past 2 decades.[2,12] Recent studies have shown a link between the development of cardiovascular disease and HIV infection with multiple potential mechanisms, including direct vascular inflammation,[13,14] dyslipidemia,[15] and insulin resistance.[16,17]

The aim of this systematic analysis was to review and to meta-analyze the rate of cardiovascular disease in people living with HIV, to determine the association between HIV infection and the risk of cardiovascular disease, and to estimate the national, regional, and global burden of HIV-associated cardiovascular disease.

METHODS

Data and the corresponding R analysis code will be available at https://github.com/anoopsshah/hiv_cvd.

Databases, Sources, and Searches

We searched MEDLINE, EMBASE, Global Health, Cumulative Index to Nursing and Allied Health Literature, and Web of Science by using the following key words: myocardial infarction, stroke, cerebrovascular disease, cardiovascular disease, and HIV (Text I in the online-only Data Supplement). Bibliographic reference lists of studies selected for inclusion in our meta-analysis and relevant review articles were manually searched (Figure 1). We limited our search to studies published between 1948 and August 30, 2016.

Selection of Articles, Extraction of Data, and Data Synthesis

All longitudinal studies, including case-control, cohort, and randomized controlled trials, were included. There were no language restrictions, and only peer-reviewed original articles were included. Many studies provided data on the same cohort at extended follow-up time points. In such cases, we selected the published study with the longest follow-up period. Data were extracted independently, and any discrepancies were adjudicated by 4 investigators (A.S.V.S., D.S., K.K.L., and S.A.). We contacted authors for additional data or clarification where required. The study methodology, results, and presentation were conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Table I in the online-only Data Supplement).[18]

Crude Rate

The pooled incident crude rates of cardiovascular disease studies were only included if they provided the number of cardiovascular events (fatal or nonfatal myocardial infarction or stroke) and the follow-up period. Crude incidence rates were pooled per 10 000 person-years and presented for all incident cardiovascular events and deaths. The analysis was substratified by etiology classified as either myocardial infarction or cerebrovascular disease, where applicable.

Risk Ratio

For estimating the pooled risk ratios of cardiovascular disease, cases were defined as any hospitalization with,

Downloaded from http://ahajournals.org by on June 17, 2024

or mortality from, cardiovascular events (fatal or nonfatal myocardial infarction or stroke) in individuals with and without HIV. Studies were also included if the outcome was defined as a cardiovascular event and included but was not exclusive to myocardial infarction or stroke. Risk ratio estimates for disease incidence and case fatality for cardiovascular events in HIV-infected populations in comparison with populations not infected by HIV were pooled and presented with 95% CIs.

Pooled risk ratio estimates were assessed for publication bias by visually assessing funnel plots and for asymmetry by using the Egger regression test.[19] The trim-and-fill method was used to adjust for selection bias attributable to potential unpublished studies or bias attributable to small-study effects.[20] Sensitivity analysis was performed by removing studies where adjustment for important confounders was omitted (Table II in the online-only Data Supplement). Across both the pooled rate and risk ratios, subgroup analysis was only performed where ≥3 estimates were available. Studies providing estimates for the risk ratio were further stratified by type of event and publication year.

Regional and Global Estimates for HIV Prevalence and Cardiovascular Disability-Adjusted Life-Years

Global and regional estimates of cardiovascular disease attributable to HIV were derived annually from 1990 to 2015.

Cardiovascular Disability-Adjusted Life-Years

National disability-adjusted life-year (DALY) estimates for cardiovascular disease (consisting of the sum of DALYs attributable to ischemic heart disease and stroke) were available from the Institute of Health Metrics and Evaluation. Countries were grouped into Joint United Nations Programme on HIV/AIDS (UNAIDS) regions (Table III in the online-only Data Supplement). The DALYs for cardiovascular disease in each country were summed to derive the regional cardiovascular burden. These data were available at 5-year intervals, from 1990 to 2015, with intervening years obtained via linear interpolation.

Regional Prevalence of HIV

Prevalence estimates for HIV were available from 1990 to 2015, for the population from 15 to 49 years of age, from UNAIDS at a global and regional level.

Population-Attributable Fraction and HIV-Attributable Cardiovascular DALYs

At the global and regional levels, we applied the HIV prevalence estimates for the 15- to 49-year age group across the entire adult population. As such, the calculated population-attributable fraction was applied to the entire adult population when calculating the cardiovascular DALYs attributable to HIV at global and regional levels.

National Estimates for HIV Prevalence and Cardiovascular DALYs

National estimates of HIV prevalence and cardiovascular burden were available from 160 and 179 countries, respectively, of the 193 United Nations member states, and both were available from 154 countries. National HIV prevalence estimates were available for the >15-years age group for 2016, and national DALY estimates for cardiovascular disease were available for 2015.

We also calculated estimates of burden in the nations with a high HIV prevalence by combining data for the UNAIDS-defined 21 Global Plan priority countries (Table III in the online-only Data Supplement).[21,22] National-level data for cardiovascular DALYs for 2015 and HIV prevalence for 2016 were available for 20 of the 21 Global Plan priority countries (Table III in the online-only Data Supplement).

Statistical Analysis

Using the pooled risk ratio for cardiovascular disease in people living with HIV and the prevalence of HIV, we estimated the population-attributable risk fraction at national, regional, and global levels. At regional and global levels, we further estimated the yearly changes in attributable risk to take into account temporal changes in the population prevalence of HIV. The population-attributable fraction for HIV for cardiovascular disease was calculated as described previously:[23,24]

$$\textit{Population Attributable Fraction}=\frac{\textit{Prevalence}*(\text{Risk Ratio}-1)}{1+\textit{Prevalence}*(\text{Risk Ratio}-1)}$$

We anticipated heterogeneity between studies when estimating both the crude incidence rates and the risk ratio because of different study designs, methods of analysis and varying adjustment, and geographical and population differences. We therefore used a random-effects model with the maximum likelihood estimator to account for both within- and between-study heterogeneity.[25] Heterogeneity, when estimating the pooled estimate of the risk ratio, was examined using the standard I^2 test. Publication or small-study bias was assessed using the regression test, and the trim-and-fill method was used for correcting funnel plot asymmetry. Risk of bias was assessed at a study level according to the level of adjustment undertaken (Table II in the online-only Data Supplement). Studies at low risk of bias were defined if adjustment of age, sex, and at least 1 other covariate was undertaken. Moderate risk was defined as adjustment of at least age or sex, and studies were classified as high-risk if no adjustment was undertaken. Full statistical methods are explained in the online-only Data Supplement (Text II in the online-only Data Supplement, Figure IA and IB in the online-only Data Supplement). All analyses were performed in R Version 3.2.3 with the estimates derived using the meta-for package. Statistical significance was taken as a 2-sided $P<0.05$.

RESULTS

A total of 80 studies were identified to estimate the rate and risk ratio of cardiovascular disease in people living with HIV. One hundred twenty-two estimates from 73 studies were used to calculate the pooled crude incident rates of fatal and nonfatal cardiovascular disease in people living with HIV (Table IV in the online-only

Downloaded from http://ahajournals.org by on June 17, 2024

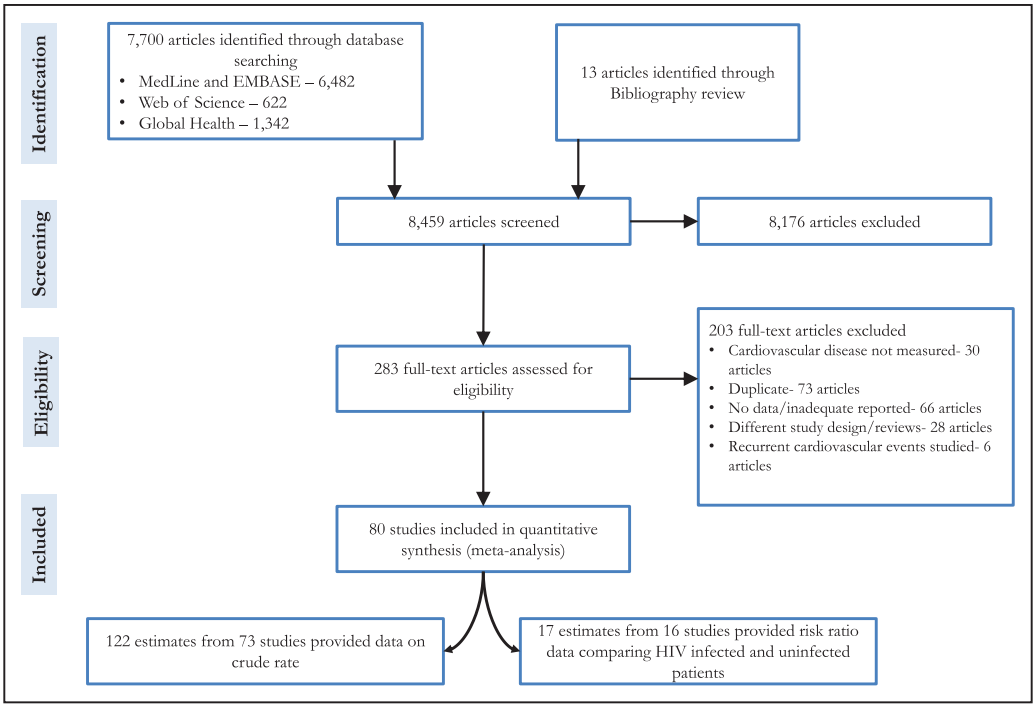

Figure 1. Flow chart.
Flow chart of studies meeting the inclusion criteria of the systematic review and meta-analysis.

Data Supplement; Figure 1). This comprised 793 635 people with HIV and a total follow-up of 3.5 million person-years. The crude incidence rate for cardiovascular disease per 10 000 person-years was 61.8 (95% CI, 45.8–83.4). When stratified by incident myocardial infarction and stroke, the rate was 25.9 (95% CI, 20.3–33.0) and 17.9 (95% CI, 13.2–24.3), respectively (Figure IIA through IIC in the online-only Data Supplement). The cardiovascular mortality rate was 14.1 per 10 000 person-years (95% CI, 10.3–19.4) (Figure IID through IIF in the online-only Data Supplement). Of the 122 estimates, only 12 (9.8%) estimates (across 11 studies) provided information on crude rates in the non-HIV population (Table V in the online-only Data Supplement).

A further 17 estimates from 16 studies were identified to estimate the pooled risk ratio of incident cardiovascular disease in individuals with HIV infection (Table, Figure 2B). Studies originated mainly from Europe, North America, and the Asia Pacific region with few studies from low- and middle-income nations (Table) and primarily involving black and white participants (Table VI in the online-only Data Supplement). The majority of studies used physician diagnosis or the *International Classification of Diseases* coding system to define cardiovascular disease. The pooled risk ratio was 2.16 (95% CI, 1.68–2.77) (Figure 2B). The risk ratio when stratified by type of event was 2.36 (95% CI, 1.50–3.70) for any cardiovascular disease (including myocardial infarction and stroke), 1.79 (95% CI, 1.54–2.08) for myocardial infarction, and 2.56 (95% CI, 1.43–4.61) for stroke. Risk ratios for older studies, those with moderate/high risk of bias, and those with longer follow-up were larger (Table VII in the online-only Data Supplement). Selection bias attributable to potential unpublished studies or to small-study effects was noticed for the overall risk ratio. Imputing for asymmetry using the trim-and-fill method did not alter the effect direction, but, as expected, did attenuate the effect size (Table VII in the online-only Data Supplement and Figure III in the online-only Data Supplement). We observed substantial heterogeneity for the overall estimate (Figure 2).

Trends in the Global and Regional Burden of Disease

Globally, the population-attributable fraction for cardiovascular disease associated with HIV infection increased from 0.36% (95% CI, 0.21%–0.56%) in 1990 to 0.92% (95% CI, 0.55%–1.41%) in 2015. This was associated with a >3-fold increase in DALYs from HIV-associated cardiovascular disease from 0.74 million (95% CI, 0.44–1.16) in 1990 to 2.57 million (95% CI, 1.53–3.92) in 2015 (Figure 3A). Similar temporal increases were seen when stratified by sex (Figure 3B, Table VIII in the online-only Data Supplement).

There was marked regional variation in the temporal change in the DALYs because of cardiovascular disease attributable to HIV (Figure 3C). In 2015, East and Southern Africa, Asia and the Pacific, and West and Central Africa accounted for over two-thirds of all DALYs (Figure 3C). The largest annual increase across the 26-

Downloaded from http://ahajournals.org by on June 17, 2024

Table. Baseline Characteristics of Studies Providing Estimates of Risk Ratio

Author	Cohort Name	Country	Study Type	Data Source	Outcome Classification	Male (%)	Age at Baseline (y)	From	To	Outcome
Qureshi et al, 1997[26]	Atlanta, GA	USA	CCS	Clinical database	ICD-9	58	35	1990	1994	Stroke*
Gardner et al, 2003[27]	HERS	USA	Cohort study	Hospital database	NA	0	38	1993	2000	CVD*†
Cole et al, 2004[28]	BW-CYSS	USA	Cohort study	Clinical database	ICD-9	83	35	1988	1991	Stroke*
Triant et al, 2009[29]	RPDR	USA	Cohort study	Clinical database	ICD-9	63	38	1997	2006	MI*
Aldaz et al, 2011[30]	Navarre, Spain	Spain	Cohort study	AIDS case register	NA	68	NA	1999	2006	CVD† (mortality)
Durand et al, 2011[31]	Quebec	Canada	Cohort study	Quebec public health insurance database and clinical database	ICD-9	78	37	NA	2007	MI*
Chow et al, 2012[32]	RPDR	USA	Cohort study	Research Patient Data Registry	ICD-9	69	42	1996	2009	Stroke (incident) *
Helleberg et al, 2012[33]‡	Danish HIV	Denmark	Cohort study	Danish Civil Registration System, National registry of cause of death	ICD-10	75.8	36	1995	2008	CVD† (mortality)
Walker et al, 2013[34]	Tanzania	Tanzania	CCS	Verbal autopsy	WHO definition	55	62	2003	2006	Stroke*
Mateen et al, 2013[35]	MACS	USA	Cohort study	MACS database	ICD-9	100	41	1996	2011	Stroke
Tripathi et al, 2014[36]	South Carolina Medicaid program	USA	Cohort study	HIV reporting system Surveillance Database	ICD-9	57	39	1994	2011	CVD*†
Womack et al, 2014[37]	VACS-VC	USA	Cohort study	Medicare/IHD Quality Enhancement Initiative	ICD-9	0	44	2003	2009	CVD† (incident)
Sico et al, 2015[38]	VACS-VC	USA	Cohort study	Medicare/IHD Quality Enhancement Initiative	ICD-9/ICD-10	100	48	2003	2009	Stroke
Rasmussen et al, 2015[39]§	Danish HIV	Denmark	Cohort study	Danish Civil Registration System, National registry of cause of death	ICD-10	76	37	1995	2014	MI (incident)
Althoff et al, 2015[40]	VACS	USA	Cohort study	Medicare/IHD Quality Enhancement Initiative	ICD-9	NA	48	2003	2010	MI*
Klein et al, 2015[41]‖	KPNC KPSC	USA	Cohort study	HIV registry; electronic medical record	ICD-9	91	41	1996	2011	MI*

CCS indicates case control study; CVD, cardiovascular disease; HIV, human immunodeficiency virus; HR, hazard ratio; ICD, *International Classification of Diseases*; MI, myocardial infarction; and NA, not available.

*Outcome data determined from hospital databases and, therefore, may exclude fatal events occurring in the community and not resulting in hospitalization.

†CVD in these studies was defined as follows: in Gardner et al[27]: ischemic heart disease, cardiomyopathy, ventricular arrhythmias, transient ischemic attack, congestive cardiac failure, deep vein thrombosis, stroke; in Aldaz et al[30]: ICD-10 codes from I00 to I99; in Helleberg et al[33]: ICD-10 codes from I00 to I99; in Tripathi et al[36]: acute myocardial infarction, angina, percutaneous intervention, and nonhemorrhagic stroke; and in Womack et al[37]: acute myocardial infarction, unstable angina, ischemic stroke, and heart failure.

‡Helleberg et al[33] provided the risk ratio for cardiovascular disease for the year of 1995 only in comparison with an age- and sex-matched reference general population.

§Rasmussen et al[39] provided a risk ratio for both myocardial infarction and stroke.

‖Klein et al[41] provided an adjusted HR of 1.4 (95% CI, 1.2–1.6) for the period of 1996 to 2011; however, this risk estimate has decreased over time to 1.0 (95% CI, 0.7–1.4) for 2010 to 2011.

year period was observed in East and Southern Africa (15 870 DALYs per year [95% CI, 7600–32 660]) with the lowest increases observed in the Middle East and North Africa (530 DALYs per year [95% CI, 280–950]) and Western and Central Europe and North America (700 DALYs per year [95% CI, 410–1070]) (Table IX in the online-only Data Supplement).

National Estimates

National estimates of prevalence and cardiovascular burden were available for 154 countries. The highest population-attributable fraction was observed in countries within sub-Saharan Africa, with HIV accounting for >15% of the cardiovascular burden in Swaziland,

Downloaded from http://ahajournals.org by on June 17, 2024

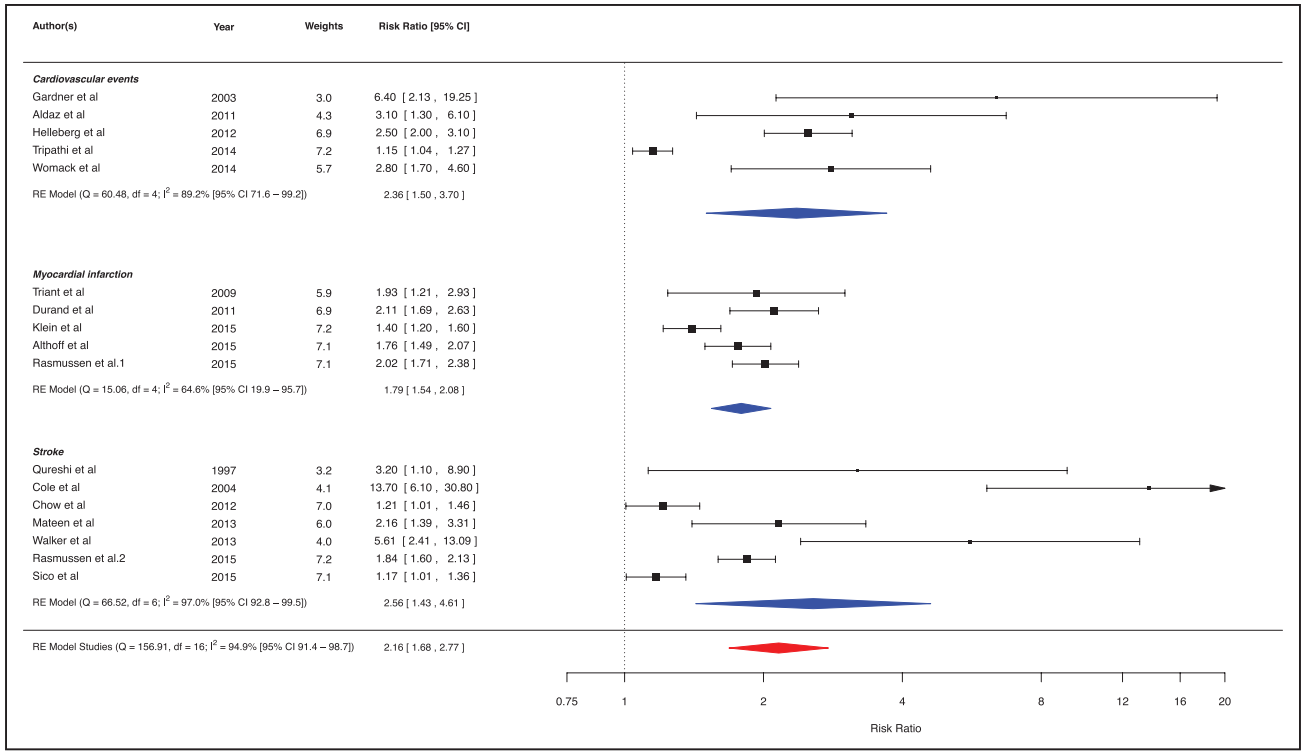

Figure 2. Forest plot.
Pooled risk ratio for risk of cardiovascular disease in people living with HIV in comparison with those without stratified by type of event.[26–41] Both Aldaz et al[30] and Helleberg et al[33] evaluated cardiovascular mortality defined as an ICD code range from I00 to I99. ICD indicates *International Classification of Diseases*; and RE, random-effects.

Downloaded from http://ahajournals.org by on June 17, 2024

Botswana, Lesotho, and South Africa (Figure 4A, Table X in the online-only Data Supplement). Similarly, the largest burden was observed in sub-Saharan Africa (Figure 4B). In the UNAIDS Global Plan priority countries, the population-attributable fraction was comparable to other traditional cardiovascular risk factors (Table XI in the online-only Data Supplement).

Data for the burden of cardiovascular DALYs attributable to HIV were available for 20 of the 21 priority countries from sub-Saharan Africa in the UNAIDS Global Plan.[22] HIV-associated cardiovascular DALYs across these countries increased from 0.21 million (95% CI, 0.11–0.38) in 1990 to 0.74 million (95% CI, 0.39–1.37) in 2015 (Figure IV in the online-only Data Supplement).

DISCUSSION

In this systematic review, meta-analysis, and burden assessment, we evaluated the association between HIV infection and cardiovascular disease, and estimated the national, regional, and global burden of cardiovascular disease attributable to HIV infection. We make a number of important and novel observations. First, the crude rate for incident cardiovascular disease was 60 per 10 000 person years and is comparable to other high-risk cardiovascular groups, such as diabetes mellitus.[42] Second, the risk of incident cardiovascular disease was 2-fold higher in people living with HIV. Third, the number of DALYs attributable to HIV-associated cardiovascular disease has increased 3-fold over the past 2 decades, but has now plateaued. Finally, there were major regional variations in both the attributable fraction and the rates of cardiovascular disease attributable to HIV, with much of the burden seen in sub-Saharan Africa, followed by Asia and the Pacific.

Many factors may have affected the estimates that we have derived and are based on several assumptions that merit discussion. First, the pooled risk ratios used to calculate the population-attributable fraction and the subsequent cardiovascular burden were primarily obtained from developed nations but were applied to all regions. This approach is ubiquitous in these types of analyses[43,44] and highlights the paucity of data from these regions. In a recent analysis evaluating the global burden of cardiovascular disease attributable to hypertension and obesity, <10% of cohorts originated from low- and middle-income nations.[44,45] Second, the incidence rate does not consider competing risk from non-cardiovascular mortality. This would further underestimate the rate of cardiovascular disease in people living with HIV, especially in earlier studies when antiretroviral therapy was not widely available. Third, although many of the individual studies evaluating the risk ratio of cardiovascular disease adjusted for important traditional risk factors, there remains the risk of residual confounding. Previous studies have already shown higher fre-

quencies of both modifiable and nonmodifiable cardiovascular risk factors in people living with HIV.[17] As such, a higher prevalence of factors that do not lie on the causal pathway may have influenced the overall association between HIV and cardiovascular events. Fourth, the pooled relative risk estimates used to calculate the

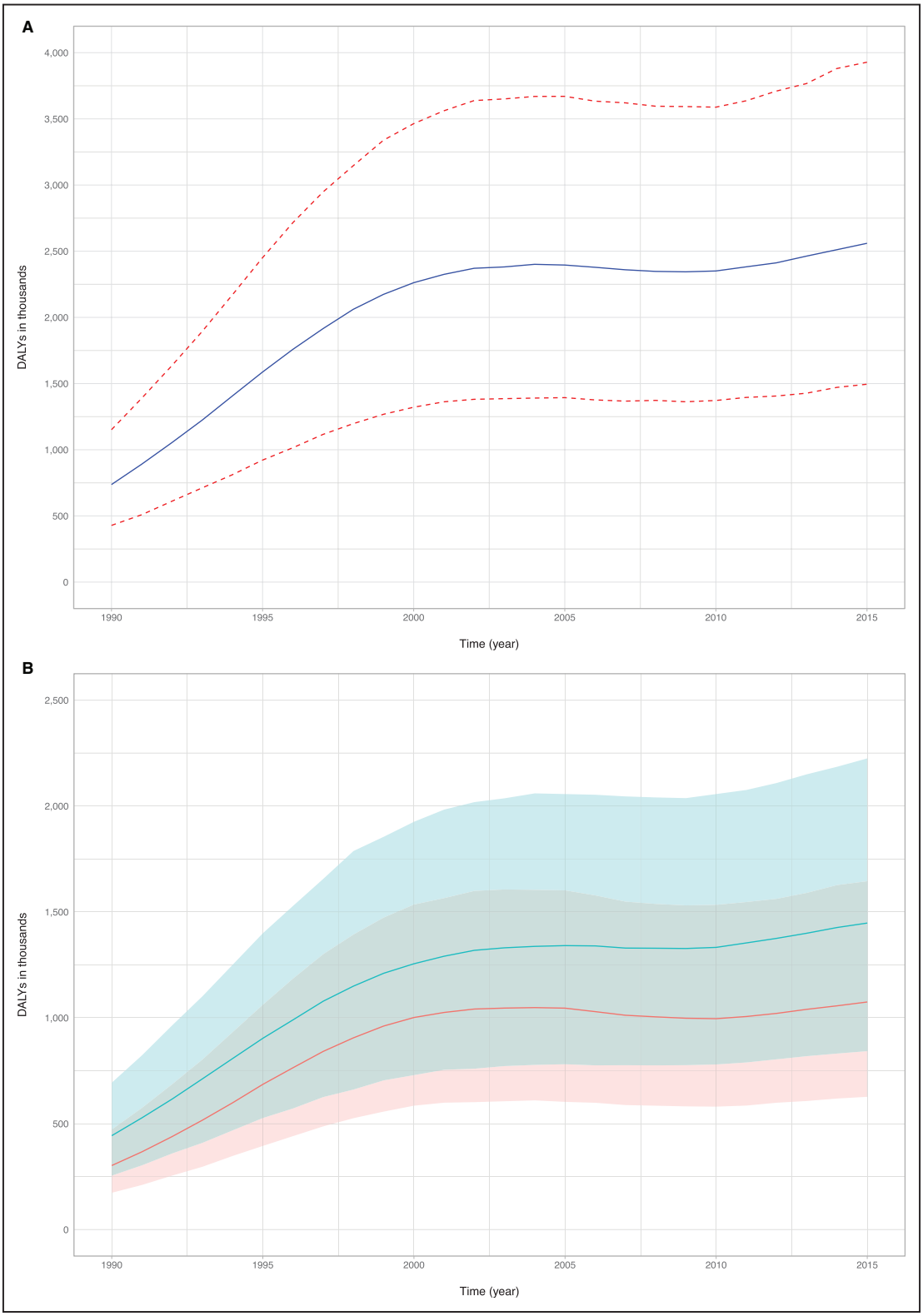

Figure 3. Disability-adjusted life-years.
Temporal change in the disability-adjusted life-years (DALYs) of HIV-associated cardiovascular disease globally (**A**) and stratified by sex (**B**); red line represents central estimate, and blue dashed lines represent the 95% CI. (*Continued*)

Downloaded from http://ahajournals.org by on June 17, 2024

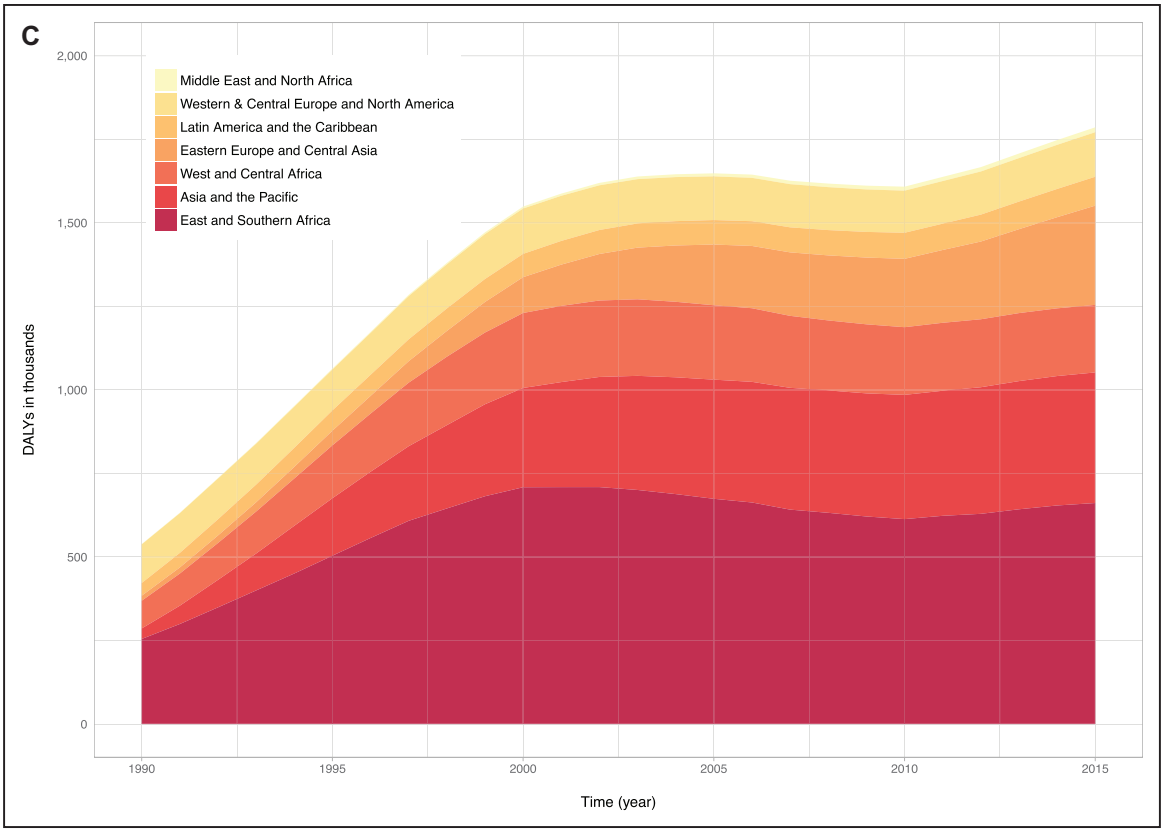

Figure 3 Continued. **C**, Stack-plot showing the central estimate by UNAIDS region and time. UNAIDS indicates Joint United Nations Programme on HIV/AIDS.

Downloaded from http://ahajournals.org by on June 17, 2024

population-attributable fraction for DALY for ischemic heart and cerebrovascular disease was obtained solely from studies including acute myocardial infarction or stroke and so did not specifically include estimates for angina pectoris or other chronic manifestations of atherosclerotic disease. However, relative to the overall cardiovascular DALY attributable to ischemic heart disease, the burden from angina is minimal.[10] Therefore, the impact of this limitation on the overall burden estimate is likely to be small. Fifth, the majority of studies evaluating the risk of cardiovascular disease in people living with HIV have recruited participants before 2010, with a large number conducted in the previous century. The epidemiology of HIV diagnosis and care has changed significantly over the past 2 decades, with better provision of antiretroviral therapy and improved survival, resulting in an increased prevalence of HIV.[46] Sixth, when calculating the burden at a global and regional level, we have made the assumption that the prevalence of HIV infection in the younger age group (15–49 years old) is consistent across the entire age range. There is a paucity of data in the prevalence of HIV in the older population, especially in high-prevalence regions such as sub-Saharan Africa.[47] However, analysis of the populations in these regions shows that the prevalence in the older population remains similar to that of the 15- to 49-year group.[47] Finally, we noticed substantial heterogeneity for our overall pooled risk ratios. The source for this degree of heterogeneity is likely to be multifactorial and reflect differences in population demographics, sample size and small-study effect, patient characteristics, selection or publication bias, and case ascertainment bias because the majority of data were based on national statistics.

Many studies have evaluated the association between HIV infection and the risk of atherosclerotic disease including the potential role of antiretroviral therapy.[17,48–50] This is the first study to review and meta-analyze systematically the association between HIV infection and cardiovascular disease, and to estimate the burden of cardiovascular disease attributable to HIV. The mechanisms underlying this association remain poorly understood.[17] Possible mechanisms include endothelial dysfunction[51] and increased systemic[13] and coronary arterial inflammation[14] associated with elevated inflammatory markers.[13] Furthermore, patients with HIV have more traditional metabolic risk factors for cardiovascular disease[17] including dyslipidemia,[15] insulin resistance and abnormal glucose homeostasis,[16] and abnormalities in body fat composition.[52–54] The increased risk of cardiovascular disease in people living with HIV is thus a consequence of both accelerated atherosclerosis attributable to chronic infection and the increased prevalence of traditional risk factors.

The global burden of cardiovascular disease attributable to HIV infection has tripled over the past 2 decades,

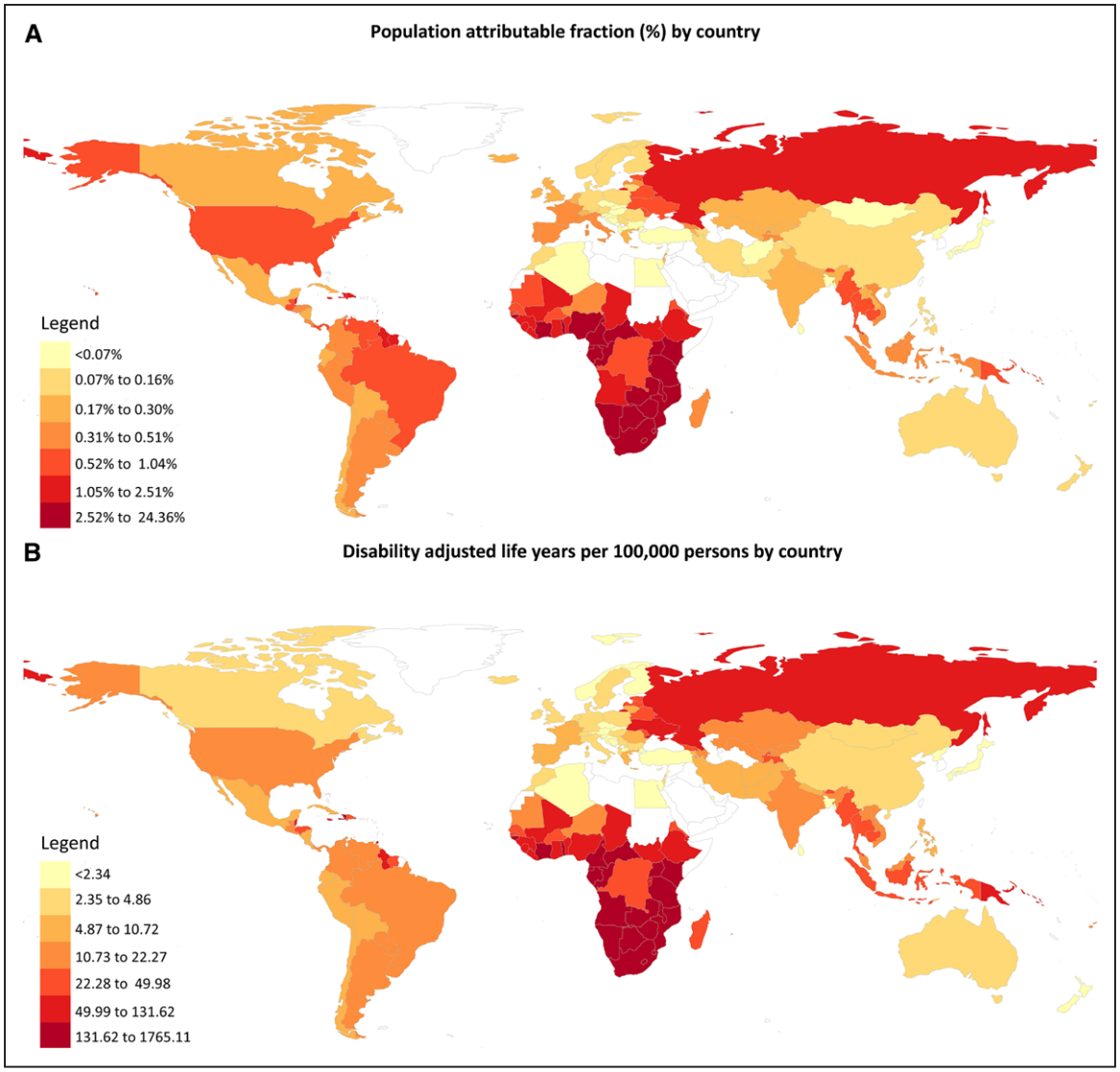

Figure 4. Cartograms.
Cartograms showing population-attributable risk (**A**) and HIV-attributable disability-adjusted life-years per 100 000 persons (**B**) for HIV-associated cardiovascular disease. Each color category represents a septile.

especially in the low- and middle-income nations, and is likely to be a product of both temporal increases in the prevalence of HIV and the morbidity and mortality from cardiovascular disease. The prevalence of HIV varies by region with the greatest proportions seen in sub-Saharan Africa and the Asia Pacific region. Cardiovascular disease now accounts for >10% of all morbidity and mortality in sub-Saharan Africa with rates that are comparable to high-income regions. Consequently, the sub-Saharan region accounted for half of all DALYs from cardiovascular disease attributable to HIV. The population-attributable fraction of HIV-associated cardiovascular disease in the UNAIDS high-priority countries was up to 25% and similar to traditional lifestyle, metabolic, and environmental risk factors.[23,24]

The combined burden of HIV and cardiovascular disease in the UNAIDS high-priority countries is of growing concern and has important implications with respect to regional health policies, guidelines, and resource allocation. Risk stratification and identification of patients at intermediate or high risk of future cardiovascular disease are already challenging in resource-limited nations.[55] Furthermore, traditional risk scores perform poorly because they consistently underestimate risk in HIV-infected populations.[35,56,57] Whether patients living with HIV should be considered high risk and started on primary prevention, such as statin therapy, remains unclear. A recent randomized controlled trial of rosuvastatin in patients with HIV demonstrated a reduction in carotid artery intima-media thickness despite these individuals having low low-density lipoprotein cholesterol concentrations at baseline.[58] Although the latest international guidelines have expanded the use of lipid-lowering therapy

Downloaded from http://ahajournals.org by on June 17, 2024

in the general population, over two-thirds of people living with HIV with evidence of high-risk morphology coronary atherosclerotic plaque would not have been recommended for statin therapy.[59] The REPRIEVE study (Randomised Trial to Prevent Vascular Events in HIV) is now underway to evaluate the efficacy of statin therapy in people living with HIV who are deemed low-risk based on traditional risk scores.[60,61]

CONCLUSIONS

This analysis evaluates the association between HIV and cardiovascular disease, and estimates the global burden of HIV-associated cardiovascular disease. We report that the risk of cardiovascular disease was 2-fold higher in people living with HIV. Moreover, the global burden of HIV-associated cardiovascular disease has tripled over the past 2 decades and is now responsible for 2.6 million DALYs per annum, with the majority in sub-Saharan Africa and the Asia Pacific regions. Our estimates have important policy implications for implementing appropriate cardiovascular risk stratification and treatment strategies across healthcare systems, especially in those countries with the greatest burden where resources remain limited.

ARTICLE INFORMATION

Received December 22, 2017; accepted June 5, 2018.

The online-only Data Supplement, podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.117.033369.

Correspondence

Anoop S.V. Shah, MD, MPH, PhD, BHF/University Centre for Cardiovascular Science, SU.305 Chancellor's Building, University of Edinburgh, Edinburgh EH16 4SB, United Kingdom. Email Anoop.Shah@ed.ac.uk

Affiliations

BHF Centre for Cardiovascular Science, University of Edinburgh, Scotland (A.S.V.S., K.K.L., S.A., S.C., F.S., D.E.N., N.L.M.). Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Scotland (A.S.V.S., H.N.)., Centre for Clinical Brain Sciences (W.W.), University of Edinburgh, United Kingdom. Joint United Nations Programme on HIV/AIDS, Geneva, Switzerland (D.S., E.J.B.). Center for Global Health, Department of Neurology, Technical University, Munich, Germany (D.S.). Division of Cardiovascular Medicine, Case Western Reserve School of Medicine, Cleveland, OH (C.T.L., S.R.). Division of Infectious Diseases and Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD (S.B., S.K.). Institute of Health and Wellbeing, University of Glasgow, United Kingdom (D.A.M.).

Acknowledgments

Dr Shah conceived the design and performed the initial acquisition, analysis, and interpretation of data. All authors were involved in drafting the manuscript and revising it, and have given final approval of the version to be published.

Sources of Funding

This research was funded by the British Heart Foundation with Dr Mills and Newby supported by the Butler Senior Clinical Research Fellowship (FS/16/14/32023) and John Wheatley Chair (CH/09/002) awards, respectively. Dr McAllister is funded via an Intermediate Clinical Fellowship and Beit Fellowship from the Wellcome Trust (201492-Z-16-Z).

Disclosures

None.

REFERENCES

1. Global AIDS Update 2016. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS. http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016. Accessed August 5, 2018.
2. Mensah GA, Roth GA, Sampson UK, Moran AE, Feigin VL, Forouzanfar MH, Naghavi M, Murray CJ; GBD 2013 Mortality and Causes of Death Collaborators. Mortality from cardiovascular diseases in sub-Saharan Africa, 1990–2013: a systematic analysis of data from the Global Burden of Disease Study 2013. *Cardiovasc J Afr*. 2015;26(2 suppl 1):S6–S10.
3. Murray CJ, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, Dansereau EA, Graetz N, Barber RM, Brown JC, Wang H, Duber HC, Naghavi M, Dicker D, Dandona L, Salomon JA, Heuton KR, Foreman K, Phillips DE, Fleming TD, Flaxman AD, Phillips BK, Johnson EK, Coggeshall MS, Abd-Allah F, Abera SF, Abraham JP, Abubakar I, Abu-Raddad LJ, Abu-Rmeileh NM, Achoki T, Adeyemo AO, Adou AK, Adsuar JC, Agardh EE, Akena D, Al Kahbouri MJ, Alasfoor D, Albittar MI, Alcalá-Cerra G, Alegretti MA, Alemu ZA, Alfonso-Cristancho R, Alhabib S, Ali R, Alla F, Allen PJ, Alsharif U, Alvarez E, Alvis-Guzman N, Amankwaa AA, Amare AT, Amini H, Ammar W, Anderson BO, Antonio CA, Anwari P, Arnlöv J, Arsenijevic VS, Artaman A, Asghar RJ, Assadi R, Atkins LS, Badawi A, Balakrishnan K, Banerjee A, Basu S, Beardsley J, Bekele T, Bell ML, Bernabe E, Beyene TJ, Bhala N, Bhalla A, Bhutta ZA, Abdulhak AB, Binagwaho A, Blore JD, Basara BB, Bose D, Brainin M, Breitborde N, Castañeda-Orjuela CA, Catalá-López F, Chadha VK, Chang JC, Chiang PP, Chuang TW, Colomar M, Cooper LT, Cooper C, Courville KJ, Cowie BC, Criqui MH, Dandona R, Dayama A, De Leo D, Degenhardt L, Del Pozo-Cruz B, Deribe K, Des Jarlais DC, Dessalegn M, Dharmaratne SD, Dilmen U, Ding EL, Driscoll TR, Durrani AM, Ellenbogen RG, Ermakov SP, Esteghamati A, Faraon EJ, Farzadfar F, Fereshtehnejad SM, Fijabi DO, Forouzanfar MH, Fra Paleo U, Gaffikin L, Gamkrelidze A, Gankpé FG, Geleijnse JM, Gessner BD, Gibney KB, Ginawi IA, Glaser EL, Gona P, Goto A, Gouda HN, Gugnani HC, Gupta R, Gupta R, Hafezi-Nejad N, Hamadeh RR, Hammami M, Hankey GJ, Harb HL, Haro JM, Havmoeller R, Hay SI, Hedayati MT, Pi IB, Hoek HW, Hornberger JC, Hosgood HD, Hotez PJ, Hoy DG, Huang JJ, Iburg KM, Idrisov BT, Innos K, Jacobsen KH, Jeemon P, Jensen PN, Jha V, Jiang G, Jonas JB, Juel K, Kan H, Kankindi I, Karam NE, Karch A, Karema CK, Kaul A, Kawakami N, Kazi DS, Kemp AH, Kengne AP, Keren A, Kereselidze M, Khader YS, Khalifa SE, Khan EA, Khang YH, Khonelidze I, Kinfu Y, Kinge JM, Knibbs L, Kokubo Y, Kosen S, Defo BK, Kulkarni VS, Kulkarni C, Kumar K, Kumar RB, Kumar GA, Kwan GF, Lai T, Balaji AL, Lam H, Lan Q, Lansingh VC, Larson HJ, Larsson A, Lee JT, Leigh J, Leinsalu M, Leung R, Li Y, Li Y, De Lima GM, Lin HH, Lipshultz SE, Liu S, Liu Y, Lloyd BK, Lotufo PA, Machado VM, Maclachlan JH, Magis-Rodriguez C, Majdan M, Mapoma CC, Marcenes W, Marzan MB, Masci JR, Mashal MT, Mason-Jones AJ, Mayosi BM, Mazorodze TT, Mckay AC, Meaney PA, Mehndiratta MM, Mejia-Rodriguez F, Melaku YA, Memish ZA, Mendoza W, Miller TR, Mills EJ, Mohammad KA, Mokdad AH, Mola GL, Monasta L, Montico M, Moore AR, Mori R, Moturi WN, Mukaigawara M, Murthy KS, Naheed A, Naidoo KS, Naldi L, Nangia V, Narayan KM, Nash D, Nejjari C, Nelson RG, Neupane SP, Newton CR, Ng M, Nisar MI, Nolte S, Norheim OF, Nowaseb V, Nyakarahuka L, Oh IH, Ohkubo T, Olusanya BO, Omer SB, Opio JN, Orisakwe OE, Pandian JD, Papachristou C, Caicedo AJ, Patten SB, Paul VK, Pavlin BI, Pearce N, Pereira DM, Pervaiz A, Pesudovs K, Petzold M, Pourmalek F, Qato D, Quezada AD, Quistberg DA, Rafay A, Rahimi K, Rahimi-Movaghar V, Ur Rahman S, Raju M, Rana SM, Razavi H, Reilly RQ, Remuzzi G, Richardus JH, Ronfani L, Roy N, Sabin N, Saeedi MY, Sahraian MA, Samonte GM, Sawhney M, Schneider IJ, Schwebel DC, Seedat S, Sepanlou SG, Servan-Mori EE, Sheikhbahaei S, Shibuya K, Shin HH, Shiue I, Shivakoti R, Sigfusdottir ID, Silberberg DH, Silva AP, Simard EP, Singh JA, Skirbekk V, Sliwa K, Soneji S, Soshnikov SS, Sreeramareddy CT, Stathopoulou VK, Stroumpoulis K, Swaminathan S, Sykes BL, Tabb KM, Talongwa RT, Tenkorang EY, Terkawi AS, Thomson AJ, Thorne-Lyman AL, Towbin JA, Traebert J, Tran BX, Dimbuene ZT, Tsilimbaris M, Uchendu US, Ukwaja KN, Uzun SB, Vallely AJ, Vasankari TJ, Venketasubramanian N, Violante FS, Vlassov VV, Vollset SE, Waller S, Wallin MT, Wang L, Wang X, Wang Y, Weichenthal S, Weiderpass E, Weintraub RG, Westerman R, White RA, Wilkinson JD, Williams TN, Woldeyohannes SM, Wong JQ, Xu G, Yang YC, Yano Y, Yentur GK, Yip P, Yonemoto N, Yoon SJ, Younis M, Yu C, Jin KY, El Sayed Zaki M, Zhao Y, Zheng Y, Zhou M, Zhu J, Zou XN, Lopez AD, Vos T. Global, re-

Downloaded from http://ahajournals.org by on June 17, 2024

gional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384:1005–1070. doi: 10.1016/S0140-6736(14)60844-8

4. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853–860. doi: 10.1056/NEJM199803263381301
5. Neuhaus J, Angus B, Kowalska JD, La Rosa A, Sampson J, Wentworth D, Mocroft A; INSIGHT SMART and ESPRIT study groups. Risk of all-cause mortality associated with nonfatal AIDS and serious non-AIDS events among adults infected with HIV. *AIDS*. 2010;24:697–706. doi: 10.1097/QAD.0b013e3283365356
6. Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, Gatell J, Rakhmanova A, Johnson M, Kirk O, Lundgren J; EuroSIDA Study Group. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. *J Acquir Immune Defic Syndr*. 2010;55:262–270. doi: 10.1097/QAI.0b013e3181e9be6b
7. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis*. 2010;50:1387–1396.
8. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA III, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–2128. doi: 10.1016/S0140-6736(12)61728-0
9. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fèvre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gonzalez-Medina D, Gosselin R, Grainger R, Grant B, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Laden F, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Levinson D, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mock C, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leòn FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiebe N, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, AlMazroa MA, Memish ZA. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2197–2223. doi: 10.1016/S0140-6736(12)61689-4
10. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, Murray CJ, Naghavi M. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. *Circulation*. 2014;129:1493–1501. doi: 10.1161/CIRCULATIONAHA.113.004046
11. Fuster V. Global burden of cardiovascular disease: time to implement feasible strategies and to monitor results. *J Am Coll Cardiol*. 2014;64:520–522. doi: 10.1016/j.jacc.2014.06.1151
12. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, Murray CJ. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation*. 2015;132:1667–1678. doi: 10.1161/CIRCULATIONAHA.114.008720
13. Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, Corsini E, Abdelbaky A, Zanni MV, Hoffmann U, Williams KC, Lo J, Grinspoon SK. Arterial inflammation in patients with HIV. *JAMA*. 2012;308:379–386. doi: 10.1001/jama.2012.6698
14. Tawakol A, Lo J, Zanni MV, Marmarelis E, Ihenachor EJ, MacNabb M, Wai B, Hoffmann U, Abbara S, Grinspoon S. Increased arterial inflammation relates to high-risk coronary plaque morphology in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2014;66:164–171. doi: 10.1097/QAI.0000000000000138
15. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab*. 1992;74:1045–1052. doi: 10.1210/jcem.74.5.1373735
16. Hadigan C, Meigs JB, Corcoran C, Rietschel P, Piecuch S, Basgoz N, Davis B, Sax P, Stanley T, Wilson PW, D'Agostino RB, Grinspoon S. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis*. 2001;32:130–139. doi: 10.1086/317541

Downloaded from http://ahajournals.org by on June 17, 2024

17. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med*. 2005;352:48–62. doi: 10.1056/NEJMra041811
18. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
20. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455–463.
21. Theodoratou E, McAllister DA, Reed C, Adeloye DO, Rudan I, Muhe LM, Madhi SA, Campbell H, Nair H. Global, regional, and national estimates of pneumonia burden in HIV-infected children in 2010: a meta-analysis and modelling study. *Lancet Infect Dis*. 2014;14:1250–1258. doi: 10.1016/S1473-3099(14)70990-9
22. 2015 Progress Report on the Global Plan. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS. http://www.unaids.org/en/ourwork/programmebranch/officeglobalplan
23. Shah AS, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, Langrish JP, Newby DE, Mills NL. Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ*. 2015;350:h1295.
24. Shah AS, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, Newby DE, Mills NL. Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet*. 2013;382:1039–1048. doi: 10.1016/S0140-6736(13)60898-3
25. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Software*. 2010;36:1–48.
26. Qureshi AI, Janssen RS, Karon JM, Weissman JP, Akbar MS, Safdar K, Frankel MR. Human immunodeficiency virus infection and stroke in young patients. *Arch Neurol*. 1997;54:1150–1153.
27. Gardner LI, Klein RS, Szczech LA, Phelps RM, Tashima K, Rompalo AM, Schuman P, Sadek RF, Tong TC, Greenberg A, Holmberg SD; HIV Epidemiology Research Study Group. Rates and risk factors for condition-specific hospitalizations in HIV-infected and uninfected women. *J Acquir Immune Defic Syndr*. 2003;34:320–330.
28. Cole JW, Pinto AN, Hebel JR, Buchholz DW, Earley CJ, Johnson CJ, Macko RF, Price TR, Sloan MA, Stern BJ, Wityk RJ, Wozniak MA, Kittner SJ. Acquired immunodeficiency syndrome and the risk of stroke. *Stroke*. 2004;35:51–56. doi: 10.1161/01.STR.0000105393.57853.11
29. Triant VA, Meigs JB, Grinspoon SK. Association of C-reactive protein and HIV infection with acute myocardial infarction. *J Acquir Immune Defic Syndr*. 2009;51:268–273. doi: 10.1097/QAI.0b013e3181a9992c
30. Aldaz P, Moreno-Iribas C, Egüés N, Irisarri F, Floristan Y, Sola-Boneta J, Martínez-Artola V, Sagredo M, Castilla J. Mortality by causes in HIV-infected adults: comparison with the general population. *BMC Public Health*. 2011;11:300. doi: 10.1186/1471-2458-11-300
31. Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Québec's public health insurance database. *J Acquir Immune Defic Syndr*. 2011;57:245–253. doi: 10.1097/QAI.0b013e31821d33a5
32. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. *J Acquir Immune Defic Syndr*. 2012;60:351–358. doi: 10.1097/QAI.0b013e31825c7f24
33. Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Gerstoft J, Obel N. Causes of death among Danish HIV patients compared with population controls in the period 1995-2008. *Infection*. 2012;40:627–634. doi: 10.1007/s15010-012-0293-y
34. Walker R, Jusabani A, Aris E, Gray W, Unwin N, Swai M, Alberti G, Mugusi F. Stroke risk factors in an incident population in urban and rural Tanzania: a prospective, community-based, case-control study. *Lancet Glob Health*. 2013;1:e282–e288.
35. Mateen FJ, Post WS, Sacktor N, Abraham AG, Becker JT, Smith BR, Detels R, Martin E, Phair JP, Shinohara RT; Multicenter AIDS Cohort Study (MACS) Investigators. Long-term predictive value of the Framingham Risk Score for Stroke in HIV-positive vs HIV-negative men. *Neurology*. 2013;81:2094–2102. doi: 10.1212/01.wnl.0000437296.97946.73
36. Tripathi A, Liese AD, Winniford MD, Jerrell JM, Albrecht H, Rizvi AA, Zhang J, Duffus WA. Impact of clinical and therapeutic factors on incident cardiovascular and cerebrovascular events in a population-based cohort of HIV-infected and non-HIV-infected adults. *Clin Cardiol*. 2014;37:517–522. doi: 10.1002/clc.22311
37. Womack JA, Chang CC, So-Armah KA, Alcorn C, Baker JV, Brown ST, Budoff M, Butt AA, Gibert C, Goetz MB, Gottdiener J, Gottlieb S, Justice AC, Leaf D, McGinnis K, Rimland D, Rodriguez-Barradas MC, Sico J, Skanderson M, Tindle H, Tracy RP, Warner A, Freiberg MS. HIV infection and cardiovascular disease in women. *J Am Heart Assoc*. 2014;3:e001035. doi: 10.1161/JAHA.114.001035
38. Sico JJ, Chang CC, So-Armah K, Justice AC, Hylek E, Skanderson M, McGinnis K, Kuller LH, Kraemer KL, Rimland D, Bidwell Goetz M, Butt AA, Rodriguez-Barradas MC, Gibert C, Leaf D, Brown ST, Samet J, Kazis L, Bryant K, Freiberg MS; Veterans Aging Cohort Study. HIV status and the risk of ischemic stroke among men. *Neurology*. 2015;84:1933–1940. doi: 10.1212/WNL.0000000000001560
39. Rasmussen LD, May MT, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, Obel N. Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study. *Lancet HIV*. 2015;2:e288–e298. doi: 10.1016/S2352-3018(15)00077-6
40. Althoff KN, McGinnis KA, Wyatt CM, Freiberg MS, Gilbert C, Oursler KK, Rimland D, Rodriguez-Barradas MC, Dubrow R, Park LS, Skanderson M, Shiels MS, Gange SJ, Gebo KA, Justice AC; Veterans Aging Cohort Study (VACS). Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. *Clin Infect Dis*. 2015;60:627–638. doi: 10.1093/cid/ciu869
41. Klein DB, Leyden WA, Xu L, Chao CR, Horberg MA, Towner WJ, Hurley LB, Marcus JL, Quesenberry CP Jr, Silverberg MJ. Declining relative risk for myocardial infarction among HIV-positive compared with HIV-negative individuals with access to care. *Clin Infect Dis*. 2015;60:1278–1280. doi: 10.1093/cid/civ014
42. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB, D'Agostino RB Sr, Wilson PW, Savage PJ. Trends in cardiovascular complications of diabetes. *JAMA*. 2004;292:2495–2499. doi: 10.1001/jama.292.20.2495
43. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Hassen Abate K, Akinyemiju TF, Ali R, Alvis-Guzman N, Azzopardi P, Banerjee A, Bärnighausen T, Basu A, Bekele T, Bennett DA, Biadgilign S, Catalá-López F, Feigin VL, Fernandes JC, Fischer F, Gebru AA, Gona P, Gupta R, Hankey GJ, Jonas JB, Judd SE, Khang YH, Khosravi A, Kim YJ, Kimokoti RW, Kokubo Y, Kolte D, Lopez A, Lotufo PA, Malekzadeh R, Melaku YA, Mensah GA, Misganaw A, Mokdad AH, Moran AE, Nawaz H, Neal B, Ngalesoni FN, Ohkubo T, Pourmalek F, Rafay A, Rai RK, Rojas-Rueda D, Sampson UK, Santos IS, Sawhney M, Schutte AE, Sepanlou SG, Shifa GT, Shiue I, Tedla BA, Thrift AG, Tonelli M, Truelsen T, Tsilimparis N, Ukwaja KN, Uthman OA, Vasankari T, Venketasubramanian N, Vlassov VV, Vos T, Westerman R, Yan LL, Yano Y, Yonemoto N, Zaki ME, Murray CJ. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA*. 2017;317:165–182. doi: 10.1001/jama.2016.19043
44. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Ärnlöv J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ, Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Fürst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang YH, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirrakhimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin MJ, Shiri R, Shiue I, Roba HS, Silva DAS, Silverberg JI, Singh JA, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, Murray CJL; GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377:13–27. doi: 10.1056/NEJMoa1614362

Downloaded from http://ahajournals.org by on June 17, 2024

45. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, Farzadfar F, Stevens GA, Lim SS, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Pressure). National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5·4 million participants. *Lancet*. 2011;377:568–577. doi: 10.1016/S0140-6736(10)62036-3
46. GBD 2015 HIV Collaborators. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the Global Burden of Disease Study 2015. *Lancet HIV*. 2016;3:e361–e387.
47. Negin J, Cumming RG. HIV infection in older adults in sub-Saharan Africa: extrapolating prevalence from existing data. *Bull World Health Organ*. 2010;88:847–853. doi: 10.2471/BLT.10.076349
48. Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med*. 2012;13:453–468. doi: 10.1111/j.1468-1293.2012.00996.x
49. Bavinger C, Bendavid E, Niehaus K, Olshen RA, Olkin I, Sundaram V, Wein N, Holodniy M, Hou N, Owens DK, Desai M. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. *PLoS One*. 2013;8:e59551. doi: 10.1371/journal.pone.0059551
50. The DADS Study Group; Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte AdA, El-Sadr W, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356:1723–1735.
51. Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, Sosman JM. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. *Circulation*. 2001;104:257–262.
52. Bernasconi E, Boubaker K, Junghans C, Flepp M, Furrer HJ, Haensel A, Hirschel B, Boggian K, Chave JP, Opravil M, Weber R, Rickenbach M, Telenti A; Swiss HIV Cohort Study. Abnormalities of body fat distribution in HIV-infected persons treated with antiretroviral drugs: the Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr*. 2002;31:50–55.
53. Lichtenstein KA, Ward DJ, Moorman AC, Delaney KM, Young B, Palella FJ Jr, Rhodes PH, Wood KC, Holmberg SD; HIV Outpatient Study Investigators. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS*. 2001;15:1389–1398.
54. Miller J, Carr A, Emery S, Law M, Mallal S, Baker D, Smith D, Kaldor J, Cooper DA. HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. *HIV Med*. 2003;4:293–301.
55. Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. *Curr Probl Cardiol*. 2010;35:72–115. doi: 10.1016/j.cpcardiol.2009.10.002
56. Friis-Møller N, Thiébaut R, Reiss P, Weber R, Monforte AD, De Wit S, El-Sadr W, Fontas E, Worm S, Kirk O, Phillips A, Sabin CA, Lundgren JD, Law MG; DAD study group. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur J Cardiovasc Prev Rehabil*. 2010;17:491–501. doi: 10.1097/HJR.0b013e328336a150
57. Bagchi S, Hickey A. Cardiovascular disease risk assessment tools in HIV-infected patients – are they adequate?. *J AIDS Clin Res* 2016;7;583.
58. Longenecker CT, Sattar A, Gilkeson R, McComsey GA. Rosuvastatin slows progression of subclinical atherosclerosis in patients with treated HIV infection. *AIDS*. 2016;30:2195–2203. doi: 10.1097/QAD.0000000000001167
59. Zanni MV, Fitch KV, Feldpausch M, Han A, Lee H, Lu MT, Abbara S, Ribaudo H, Douglas PS, Hoffmann U, Lo J, Grinspoon SK. 2013 American College of Cardiology/American Heart Association and 2004 Adult Treatment Panel III cholesterol guidelines applied to HIV-infected patients with/without subclinical high-risk coronary plaque. *AIDS*. 2014;28:2061–2070. doi: 10.1097/QAD.0000000000000360
60. Gilbert JM, Fitch KV, Grinspoon SK. HIV-related cardiovascular disease, statins, and the REPRIEVE Trial. *Top Antivir Med*. 2015;23:146–149.
61. Mitka M. Exploring statins to decrease HIV-related heart disease risk. *JAMA*. 2015;314:657–659. doi: 10.1001/jama.2015.5498

Downloaded from http://ahajournals.org by on June 17, 2024