Journal of the American Heart Association

ORIGINAL RESEARCH

Viral Infections and Risk of Cardiovascular Disease: Systematic Review and Meta-Analysis

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BACKGROUND: We conducted a systematic review and meta-analysis of studies examining the association of viral infections with the risk of cardiovascular disease, including coronary heart disease (CHD) and stroke.

METHODS: MEDLINE, Embase, Web of Science, African-Wide Information, and the Cochrane Library database were searched from inception to July 2024.

RESULTS: We included 155 studies. HIV infection was consistently associated with an elevated risk of CHD (pooled adjusted risk ratio [RR], 1.60 [95% CI, 1.38–1.85]) and stroke (RR, 1.45 [95% CI, 1.26–1.67]). SARS-CoV-2 infection was associated with an increased risk of CHD (RR, 1.74 [95% CI, 1.44–2.11]) and stroke (RR, 1.69 [95% CI, 1.23–2.31]). In self-controlled case series studies, laboratory-confirmed influenza infection was associated with an elevated risk of acute myocardial infarction (pooled incidence rate ratio, 4.01 [95% CI, 2.66–6.05]) and stroke during the first 1 month (incidence rate ratio, 5.01 [95% CI, 3.41–7.37]). In cohort studies, hepatitis C virus infection was associated with a higher risk of CHD (RR, 1.27 [95% CI, 1.13–1.42]) and stroke (RR, 1.23 [95% CI, 1.04–1.46]). Herpes zoster was also associated with an elevated risk of CHD (RR, 1.12 [95% CI, 1.08–1.15]) and stroke (RR, 1.18 [95% CI, 1.09–1.27]). There is insufficient evidence to determine the effect of cytomegalovirus on cardiovascular disease. Although on a limited basis, hepatitis A virus, herpes simplex virus type 1, respiratory syncytial virus, human papillomavirus, dengue, and chikungunya have been linked to an increased risk of cardiovascular disease.

CONCLUSIONS: Influenza, SARS-CoV-2, HIV, hepatitis C virus, and herpes zoster were associated with an increased risk of major cardiovascular events. Vaccines may play an important role in preventing the risk of cardiovascular disease.

Key Words: cardiovascular diseases ■ infection ■ myocardial infarction ■ stroke ■ virus

Cardiovascular diseases (CVD) are the leading cause of death worldwide, accounting for 20.5 million deaths in 2021.[1] Over the past several decades, CVD morbidity and death have increased significantly in low- and middle-income countries, which now account for >80% of CVD-related deaths globally.

Viral infections increase an acute inflammatory response, which leads to elevated levels of proinflammatory cytokines, endothelial dysfunction, hypercoagulable state, and possibly rupture of atherosclerotic plaques.[2–5] During the COVID-19 pandemic, it became evident that SARS-CoV-2 infection increases the risk of stroke and acute myocardial infarction (MI). Numerous studies have investigated the association between other viral infections and CVD over the past several decades, although the findings for some viruses remain inconclusive.[6–8]

There is a lack of comprehensive assessments of epidemiologic studies examining the association between viral infections and the risk of CVD. Previous reviews have focused on specific viruses.[9–12] Additionally,

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This manuscript was sent to Yen-Hung Lin, MD, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.042670

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Acute respiratory infections, including influenza and SARS-CoV-2, were associated with an elevated risk of acute myocardial infarction and stroke.
- Chronic viral infections, including HIV, hepatitis C virus, and herpes zoster, were associated with a persistent increased risk of coronary heart disease and stroke in long-term cohort studies.

What Are the Clinical Implications?

- Preventive measures against viral infections, including vaccination, may reduce the risk of major cardiovascular events and enhanced efforts are required to increase the uptake of vaccines globally.
- Further research is needed for cytomegalovirus, herpes simplex virus type 1, hepatitis A virus, human papillomavirus, respiratory syncytial virus, dengue, chikungunya, and other viral infections.

Nonstandard Abbreviations and Acronyms

SCCS	self-controlled case series

prior reviews primarily examined the risk of stroke and lacked an understanding of the effects on the risk of coronary heart disease (CHD).[6,11,13] Therefore, we performed a systematic review and meta-analysis of epidemiologic studies examining the association of viral infections with the risk of CVD, including CHD and stroke.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered the study protocol in the International Prospective Register of Systematic Reviews (CRD42024564888). The authors declare that all supporting data are available within the article and its online supplementary files.

Search Strategy and Selection Criteria

We conducted a literature search using MEDLINE, Embase, Web of Science, African-Wide Information, and the Cochrane Library database, covering the period from the database's inception to July 3, 2024, with no language restrictions. The search syntax was developed by combining Medical Subject Headings terms and text words in the title and abstract around the concepts of viruses and cardiovascular disease (Data S1). We consulted with a librarian to refine the search strategy. All records were screened using Rayyan software (Rayyan Systems, Inc.).

We included studies examining the association of any viral infection with the risk of CVD. The outcome of interest was CVD, which was defined as a composite of cardiovascular death, stroke, and coronary heart disease. We included studies reporting CVD, CVD death, coronary heart disease, stroke (ischemic and hemorrhagic stroke), and heart failure. We included cohort, case–control, case–cohort, case-crossover, and self-controlled case series (SCCS) studies that reported measures of association. We excluded cross-sectional studies and ecological studies. We also excluded studies with no appropriate comparator group and studies among children only or specific clinical groups. Case reports, case series, reviews, conference abstracts, and animal studies were excluded.

We first screened titles and abstracts for eligible studies. The full texts of these potentially eligible studies were retrieved and assessed for eligibility by the 3 investigators. We also manually searched the references cited by the prior review articles for additional references. We collected information regarding the study setting and years, study design, study population, sample size, duration of follow-up, exposure definition, outcome definition, measures of association, and confounding factors adjusted in the multivariable regression model. We considered 4 domains in assessing the risk of bias in each study: (1) exposure assessment, (2) outcome assessment, (3) confounding bias, and (4) selection bias (Data S2).

Statistical Analysis

We used the DerSimonian–Laird random effects modeling approach with inverse variance weighting to estimate the pooled adjusted risk ratios (RRs) and their respective 95% CIs. The natural logarithms of the RRs and their corresponding standard errors from individual studies were used to compute the pooled estimates. Pooled incidence rate ratio (IRR) was estimated for studies using the SCCS method. For SCCS studies, we used 3-level random-effects models to account for dependencies among multiple-effect estimates within the same study. We separated studies by study design (ie, cohort studies, case–control/case–cohort studies, or SCCS studies) and reported the pooled effect estimates by study design. When the risk of an outcome is low (<10%), odds ratio and hazard ratio (HR) approximate RR; thus, we pooled these effect measures without converting them to RR. We conducted a meta-analysis when at least 3 studies

evaluated the specific virus on the same outcome. For studies that used the same study population, we included only studies of longer duration periods or the most recent study in the meta-analysis. We assessed the I^2 statistic, which estimates the proportion of the total variation among studies due to heterogeneity rather than chance. We also reported the variance of the study effects (τ^2) to assess between-study heterogeneity. To investigate the sources of heterogeneity, we conducted subgroup analyses for cohort studies based on the average duration of follow-up (<5 years versus ≥5 years) and whether studies adequately adjusted for important confounding factors. Univariate random-effects meta-regression was also performed to examine the influence of the average duration of follow-up on the association between viral infection and CVD. To evaluate possible publication bias, we inspected the funnel plot for asymmetry and performed Begg's rank correlation test when there were at least 10 studies. Sensitivity analyses were performed to assess the robustness of our findings by excluding 1 study at each analysis (leave-1-out analysis) and also excluding studies reporting odds ratio as measures of effect. All statistical analyses were conducted using R version 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 52 336 studies screened, we included 155 studies (Figure 1). The characteristics of the included studies are described in Tables S1 through S10. Of the 155 studies, 105 were cohort studies, 31 were case–control studies, 2 were case–cohort studies, 15 were SCCS studies, and 2 used both SCCS and cohort studies. Most (137) studies evaluated 1 viral infection, whereas 18 studies evaluated multiple viral infections (≥2 viruses). Most studies were conducted in North America (67 studies), Europe (46 studies), and East Asia (32 studies). The quality assessment of the included studies is described in Table S11. Approximately 71% of studies adjusted for important confounding factors (age, sex, and traditional cardiovascular risk factors) and considered low risk of confounding bias. A list of adjusted variables in the multivariable model is summarized in Tables S1 through S10.

We identified 36 studies on HIV infection.[14–49] We included 29 studies in the meta-analysis after excluding 7 studies from the same cohorts. Among 7 cohort studies, all of them found that individuals with HIV have a higher risk of CVD than those without HIV (pooled RR, 1.65 [95% CI, 1.29–2.11]; Figure 2). HIV infection was consistently associated with elevated risks of CHD (9 cohort studies; pooled RR, 1.60 [95% CI, 1.38–1.85]), stroke (9 cohort studies; pooled RR, 1.45 [95% CI, 1.26–1.67]), and heart failure (6 cohort studies; pooled RR, 1.89 [95% CI, 1.46–2.44]). In a subgroup analysis of cohort studies with a mean follow-up period of ≥5 years, HIV remained associated with a higher risk of CVD, CHD, and stroke (Figures S1 and S2 and Table S12). Results were robust after excluding studies with inadequate adjustment for confounding factors (Figure S3) and in sensitivity analyses. The funnel plots did not appear to show evidence of publication bias (Figure S4).

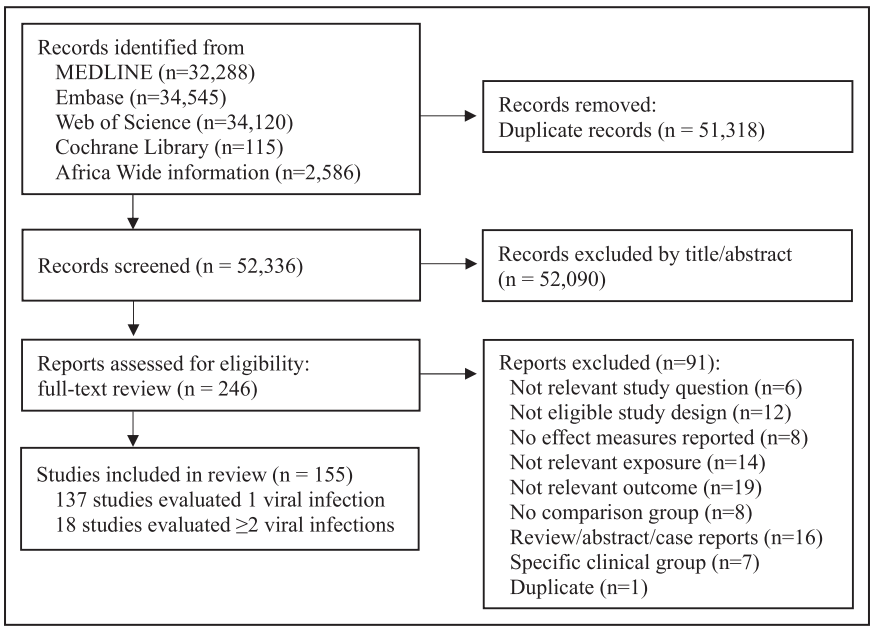

Figure 1. Flow diagram of the study selection.

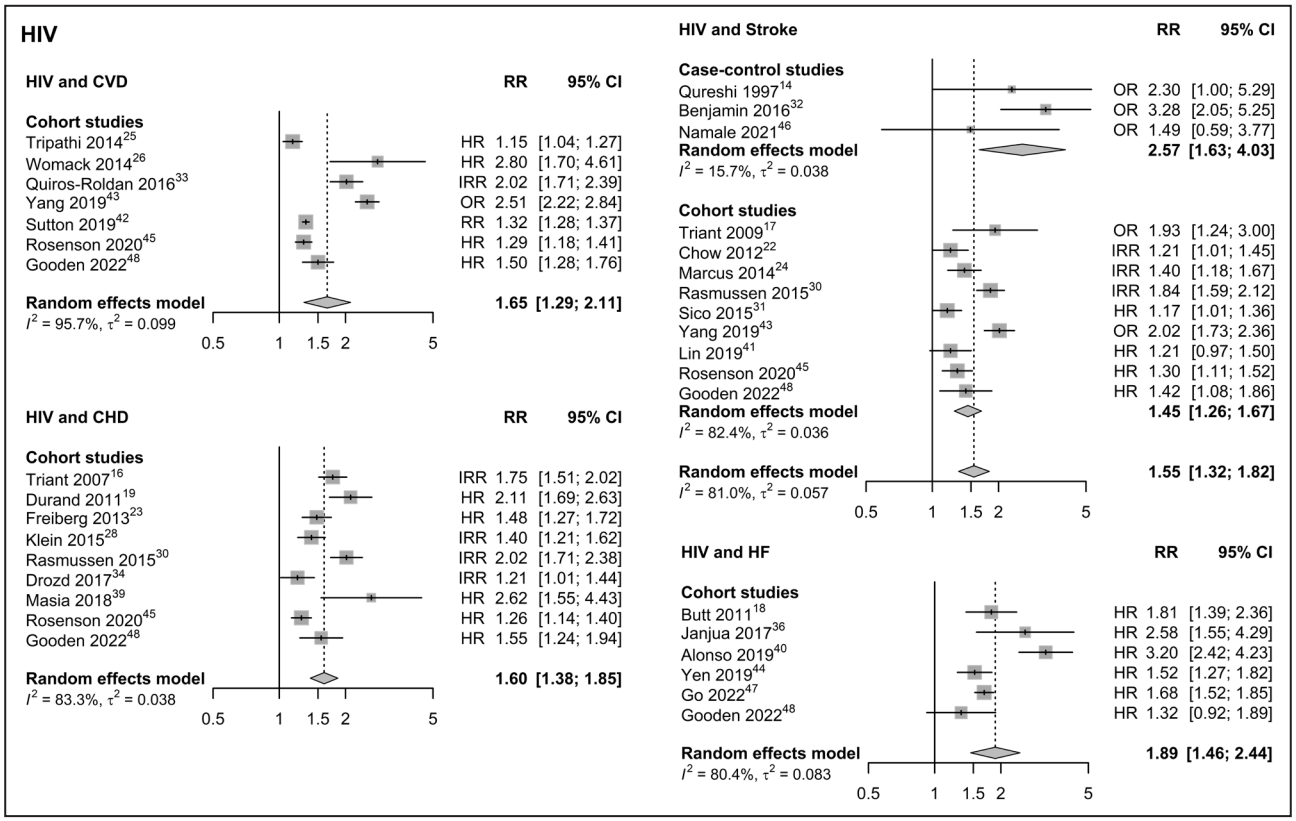

Figure 2. HIV and the risk of cardiovascular disease.

A total of 17 studies on SARS-CoV-2 infection were included (3 self-controlled case series and 14 cohort studies).[50–66] Three SCCS studies reported an elevated risk of acute MI and stroke during the first 14 weeks following SARS-CoV-2 infection (pooled IRR for MI, 3.35 [95% CI, 1.70–6.61]; and pooled IRR for stroke, 3.36 [95% CI, 1.43–7.91]; Figure 3). In cohort studies, SARS-CoV-2 infection was also associated with an increased risk of CVD (11 cohorts; pooled RR, 1.82 [95% CI, 1.44–2.30]), CHD (12 cohorts; pooled RR, 1.74 [95% CI, 1.44–2.11]), and stroke (12 cohorts; pooled RR, 1.69 [95% CI, 1.23–2.31]). However, there was evidence of between-study heterogeneity, as indicated by high τ^2 and I^2 heterogeneity. Results showed consistency in the sensitivity analyses. Although a few studies fell outside the funnel plot boundaries, there was no clear evidence of publication bias for studies on SARS-CoV-2 infection (Figure S5).

We identified 9 studies on laboratory-confirmed influenza infection (7 SCCS and 2 case–control studies).[67–75] In SCCS studies, laboratory-confirmed influenza infection was associated with an increased risk of acute MI and stroke (Figure 4). The pooled IRR for MI during the first month after influenza infection compared with the control period was 4.01 (95% CI, 2.66–6.05) in 6 studies. The risk of MI varied by risk period (test for subgroup differences, P<0.001). The pooled IRR was 7.20 (95% CI, 6.30–8.22) during the first 7 days and 1.87 (95% CI, 1.10–3.17) during days 8 to 14. Three SCCS studies reported an elevated risk of stroke in the first month following influenza infection (pooled IRR, 5.01 [95% CI, 3.41–7.37]).

Four studies on hepatitis A virus (2 cohort and 2 case–control studies) were included.[76–79] One study reported no association between hepatitis A virus and the risk of CVD (HR, 1.01 [95% CI, 0.83–1.24]). Three studies found that hepatitis A virus infection was associated with an increased risk of CHD (pooled RR, 3.80 [95% CI, 1.28–11.28]; Figure 5).

We included 9 studies on hepatitis B virus (8 cohort and 1 case–control studies).[80–88] None of the studies on hepatitis B virus infection found any positive association with the risk of CVD, CHD, or stroke (Figure 5).

A total of 31 studies investigated hepatitis C virus (HCV). We included 26 studies (21 cohort and 5 case–control) in the meta-analysis after excluding 5 studies from the same cohorts. After pooling 8 cohort studies, HCV infection was associated with an elevated risk of CVD (pooled RR, 1.39 [95% CI, 1.08–1.79]; Figure 6). Patients with HCV infection had a 2-fold higher risk of CVD death than those without HCV (3 cohort studies; pooled RR, 2.11 [95% CI, 1.62–2.74]). HCV infection

*References [20, 23, 25, 26, 81, 82, 84, 89–112].

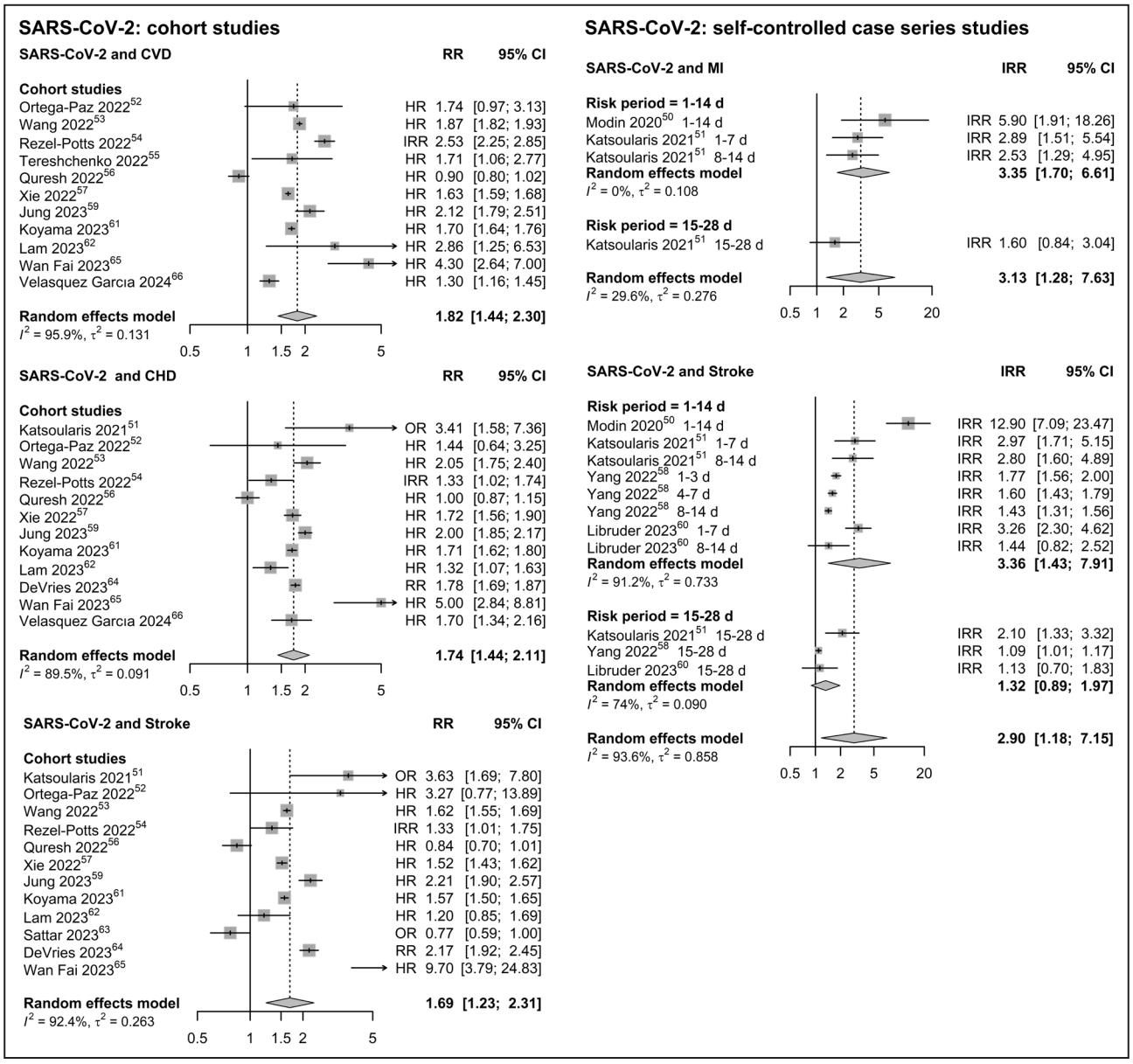

Figure 3. SARS-CoV-2 and the risk of cardiovascular disease.

was associated with a higher risk of developing CHD (10 cohort studies; RR, 1.27 [95% CI, 1.13–1.42]) and stroke (3 cohort studies; RR, 1.23 [95% CI, 1.04–1.46]). In a subgroup analysis of cohort studies with a mean follow-up period of ≥5 years, HCV was associated with a higher risk of CHD (Figures S6 and S7 and Table S13). All studies on HCV adequately adjusted for confounding factors (Figure S8). Results remained consistent in the sensitivity analyses. The funnel plot did not suggest any potential publication bias for studies on HCV (Figure S9).

We identified 30 studies on cytomegalovirus (14 cohort and 16 case–control/case–cohort studies).[76–78,113–139] Cytomegalovirus infection was based on immunoglobulin G seropositivity. Cytomegalovirus seropositivity was not associated with a risk of CVD (8 studies; pooled RR, 1.13 [95% CI, 0.90–1.43]; Figure 7). However, in a meta-analysis of 6 cohort studies, cytomegalovirus seropositive individuals had a higher risk of CVD death than the seronegative individuals (pooled RR, 1.28 [95% CI, 1.02–1.60]). Cytomegalovirus infection was associated with an increased risk of CHD in the meta-analysis of 12 case–control studies (pooled RR, 1.44 [95% CI, 1.12–1.85]) but not in 4 cohort studies (pooled RR, 1.08 [95% CI, 0.98–1.20]). cytomegalovirus infection was not associated with the risk of stroke (6 studies; pooled RR, 1.38 [95% CI, 0.80–2.36]). We noted a minor asymmetry in the funnel plot for CHD

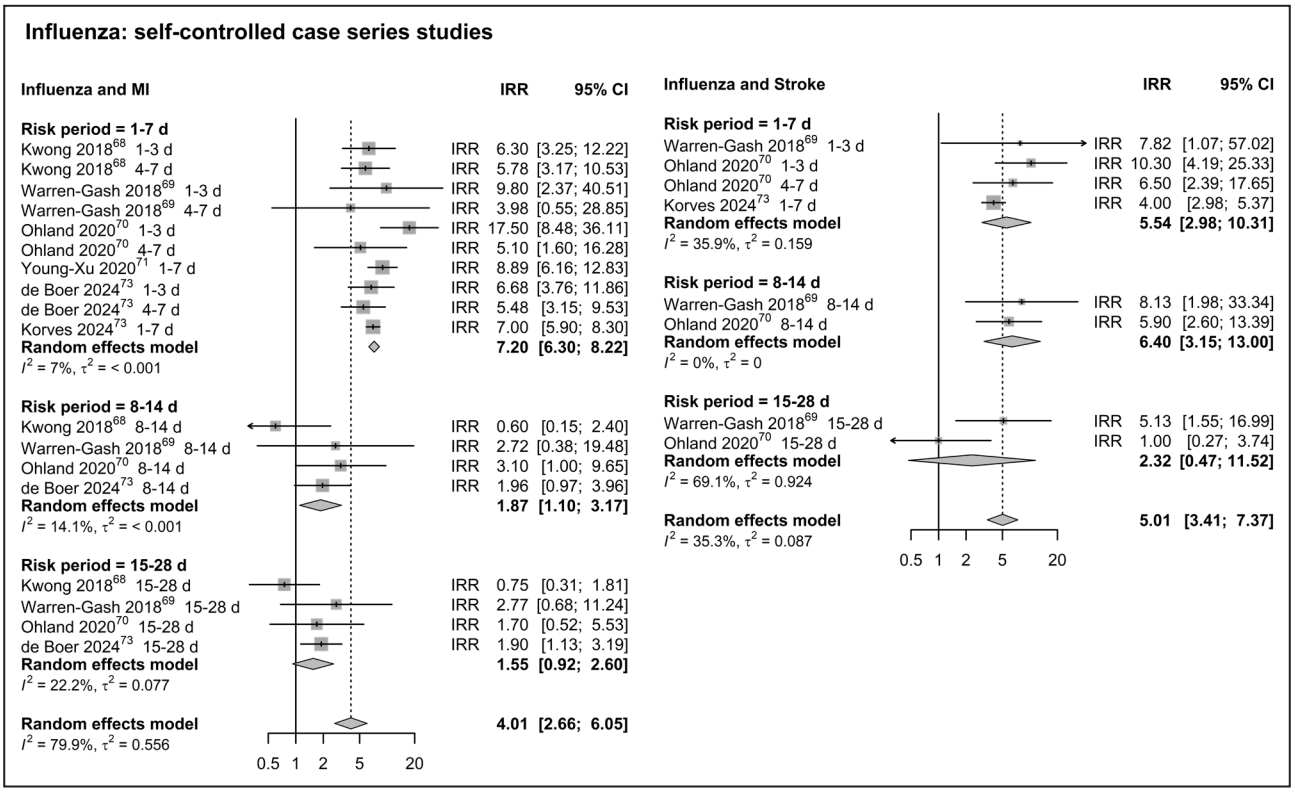

Figure 4. Influenza and the risk of cardiovascular disease.

(Figure S10); however, the asymmetry diminished after separating case–control studies and cohort studies (Begg's test was *P*=0.07 for case–control and *P*=0.60 for cohort studies).

There were 20 studies investigating herpes zoster, which results from the reactivation of varicella-zoster virus (VZV).[140–159] We included 18 studies (3 self-controlled case series, 12 cohort, and 3 case–control studies) in the meta-analysis. Three self-controlled case series studies demonstrated that herpes zoster increased the risk of stroke during the first 3 months (1–3 weeks after zoster: pooled IRR, 1.61 [95% CI, 1.41–1.84]; 5–12 weeks: IRR, 1.24 [95% CI, 1.12–1.38]; Figure S11). After pooling 4 cohort studies, herpes zoster was associated with an increased risk of CVD (4 studies; pooled RR, 1.31 [95% CI, 1.07–1.61]; Figure 8). Herpes zoster was associated with an increased risk of CHD (6 cohort studies; pooled RR, 1.12 [95% CI, 1.08–1.15]) and stroke (10 cohort studies; pooled RR, 1.18 [95% CI, 1.09–1.27]). In a subgroup analysis of cohort studies with a mean follow-up period of ≥5 years, herpes zoster remained associated with a higher risk of CHD and stroke (Figures S12 and S13 and Table S14). Robustness of the results was confirmed through subgroup analysis (Figure S14) and sensitivity analyses. We observed an asymmetry in the funnel plot for stroke; however, it was less evident after separating case–control and cohort studies (Begg's test was *P*=0.18 for cohort studies; Figure S15).

We identified 11 studies of herpes simplex virus type 1 (HSV-1) (3 cohort studies and 8 case–control studies).[†] After pooling 8 studies, HSV-1 immunoglobulin G seropositivity was associated with a higher risk of CHD (pooled RR, 1.56 [95% CI, 1.00–2.45]; Figure 7). However, there was a substantial between-study heterogeneity (I^2=69% and τ^2=0.24). Two studies did not find an association of HSV-1 with the risk of stroke. A cohort study from the UK did not find an association of HSV-1 with the risk of CVD (HR, 0.93 [95% CI, 0.72–1.22]).

A study from Brazil using the SCCS method found that in the first 28 days after chikungunya virus disease onset, there was an increased risk of death from CVD (IRR, 2.73 [95% CI, 1.50–4.96]) and ischemic heart disease (IRR, 2.38 [95% CI, 1.33–4.26]).[162]

Two studies from Taiwan evaluated dengue.[163,164] Dengue fever was associated with an elevated risk of stroke (HR, 1.16 [95% CI, 1.01–1.32]) in a cohort study.[163] The elevated risk of major cardiovascular events was observed during the first week after dengue virus infection in a study using the SCCS method (IRR, 17.9 [95% CI, 15.8–20.4]).[164]

[†]References [77, 79, 113, 118, 119, 125, 126, 130, 160, 161].

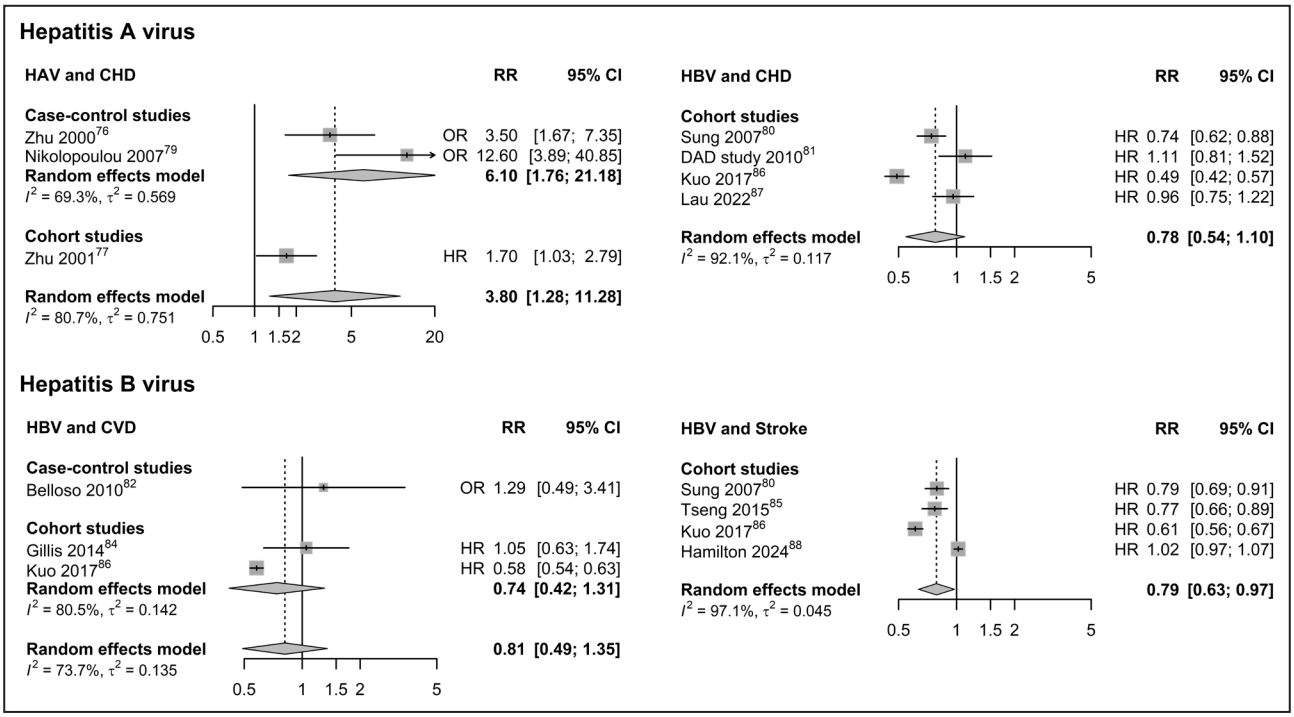

Figure 5. Hepatitis A virus/hepatitis B virus and the risk of cardiovascular disease.

A study from Sweden used the SCCS method and evaluated hemorrhagic fever with renal syndrome resulting from hantavirus infection.[165] Elevated risk of an acute MI (IRR, 5.5 [95% CI, 2.6–11.8]) and stroke (IRR, 6.0 [95% CI, 3.0–12.3]) occurred following the first 21 days of disease onset.[165]

Two cohort studies of women from South Korea investigated high-risk strains of human papillomavirus (HPV) infection.[166,167] High-risk HPV infection was associated with an increased risk of incident CVD (HR, 1.25 [95% CI, 1.03–1.52]) and CVD death (HR, 3.91 [95% CI, 1.85–8.26]).[166,167]

Three studies on herpes simplex virus type 2 were identified.[76,77,125] Two studies did not find an association of herpes simplex virus type 2 seropositivity with CHD (odds ratio, 1.90 [95% CI, 0.96–3.78]; and HR, 1.60 [95% CI, 0.88–2.90]).[76,77] A cohort study reported no association of herpes simplex virus type 2 with the risk of stroke (HR, 1.59 [95% CI, 0.91–2.76]).[125]

A case–control study of 565 patients reported that parvovirus B19 immunoglobulin G positivity was associated with coronary artery disease.[168]

One case–control study and 2 studies of SCCS examined respiratory syncytial virus (RSV) infection.[68,73,126] A case–control study of 252 patients reported that RSV was associated with a higher risk of MI (odds ratio, 11.1 [95% CI, 3.3–29.5]).[126] Two studies using SCCS consistently found an elevated risk of acute MI during the 7 days after laboratory confirmation of RSV infection (IRR, 3.38 [95% CI, 1.07–10.71]; and IRR, 3.51 [95% CI, 1.11–11.12]).[68,73]

DISCUSSION

This is the first systematic review comprehensively assessing viral infections associated with the risk of CVD from 155 studies. Influenza and SARS-CoV-2 infections were associated with elevated risk of acute cardiovascular events. Chronic viral infections, including HIV, HCV, and herpes zoster, were associated with a long-term increased risk of CHD and stroke in cohort studies. Cytomegalovirus, HSV-1, hepatitis A virus, HPV, RSV, dengue, and chikungunya have been linked to an increased risk of CVD but require more research.

Viral infections can increase the risk of stroke and CHD through direct and indirect mechanisms.[2,5,169,170] Some viruses, including HIV, COVID-19, VZV, and cytomegalovirus, directly invade arterial endothelial cells, which leads to endothelial dysfunction, smooth muscle cell proliferation, and elevated levels of proinflammatory cytokines. For example, VZV can directly invade arteries, producing VZV vasculopathy, and leading to pathologic vascular remodeling and destabilization of preexisting atherosclerotic plaques, making them vulnerable to rupture.[171] Viral infections can also indirectly accelerate the progression of atherosclerosis through the induction of proinflammatory cytokines, such as interleukin-6, and tumor necrosis factor-α, which in turn

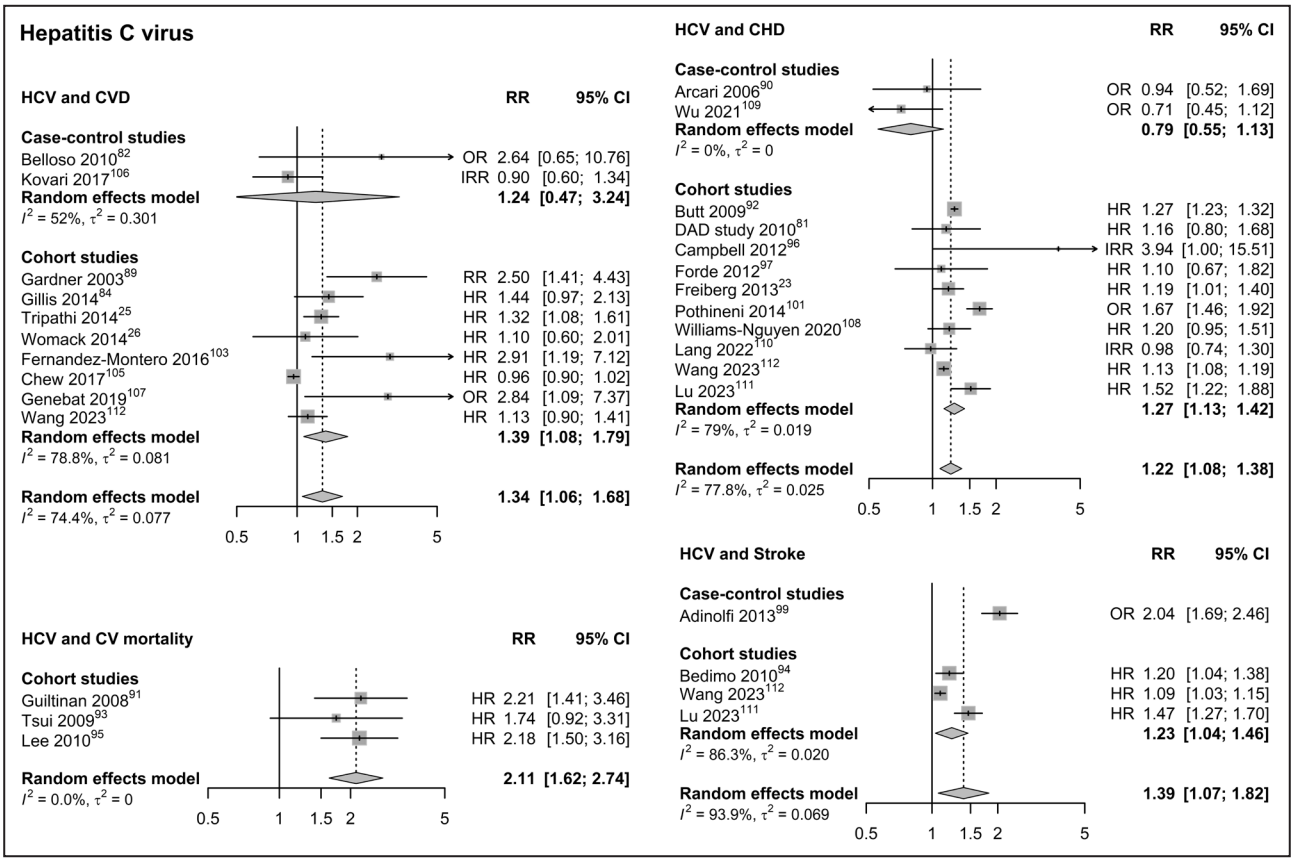

Figure 6. Hepatitis C virus and the risk of cardiovascular disease.

activate procoagulant pathways. Chronic inflammation and hypercoagulability can persist long after the clinical resolution of an acute infection. Furthermore, excessive formation of neutrophil extracellular trap has been recently recognized as a key role in triggering acute MI in patients with COVID-19.[172,173] Neutrophil extracellular trap formation is an important innate defense against infection; however, its dysregulation can exacerbate inflammation and activate the procoagulant state by increasing platelet activation and fibrin formation, contributing to thrombosis and the progression of atherosclerotic lesions.

Elevated risk of acute MI and stroke following laboratory-confirmed influenza was consistently demonstrated in studies using the rigorous self-controlled case series design. The major advantage of this study design is that it eliminates all time-invariant confounding factors, such as baseline cardiovascular risk factors and genetic factors, by having individuals serve as their own controls. Studies were based on laboratory-confirmed influenza. This implies that the results may apply to only severe cases, as physicians are more likely to request laboratory testing for only severe cases. Our study highlights the importance of prevention. Influenza vaccination was associated with a 34% lower risk of major adverse cardiovascular events in the meta-analysis of 6 clinical trials.[174] Moreover, the SCCS design has also been used in studies of SARS-CoV-2 infection, demonstrating the elevated risk of acute MI and stroke within 14 days following infection. The association of SARS-CoV-2 infection with the risk of CVD was also confirmed in cohort studies with a follow-up of up to 1 year. RSV has also been reported to have an elevated risk of acute MI during the 7 days after infection in a limited number of studies (2 SCCS studies). Nearly 22% of hospitalized adults aged 50 years or older with RSV infection experienced an acute cardiac event in a recent cross-sectional study.[175]

HIV was associated with an increased risk of CHD, stroke, and heart failure, consistent with prior reviews.[9] Even after the initiation of antiretroviral therapy, people with HIV have high levels of biomarkers of inflammation (interleukin-6), monocyte activation, and thrombosis (D-dimer).[176,177] Statin therapy not only lowers low-density lipoprotein cholesterol but also reduces inflammation and immune activation, and importantly, statins have been shown recently to be beneficial in people living with HIV. In a pivotal trial, pitavastatin treatment reduced the risk of cardiovascular events by 35% over a median follow-up of 5 years among individuals with HIV.[178] Despite nearly 70% of people living with HIV residing in sub-Saharan Africa and the prevalence of

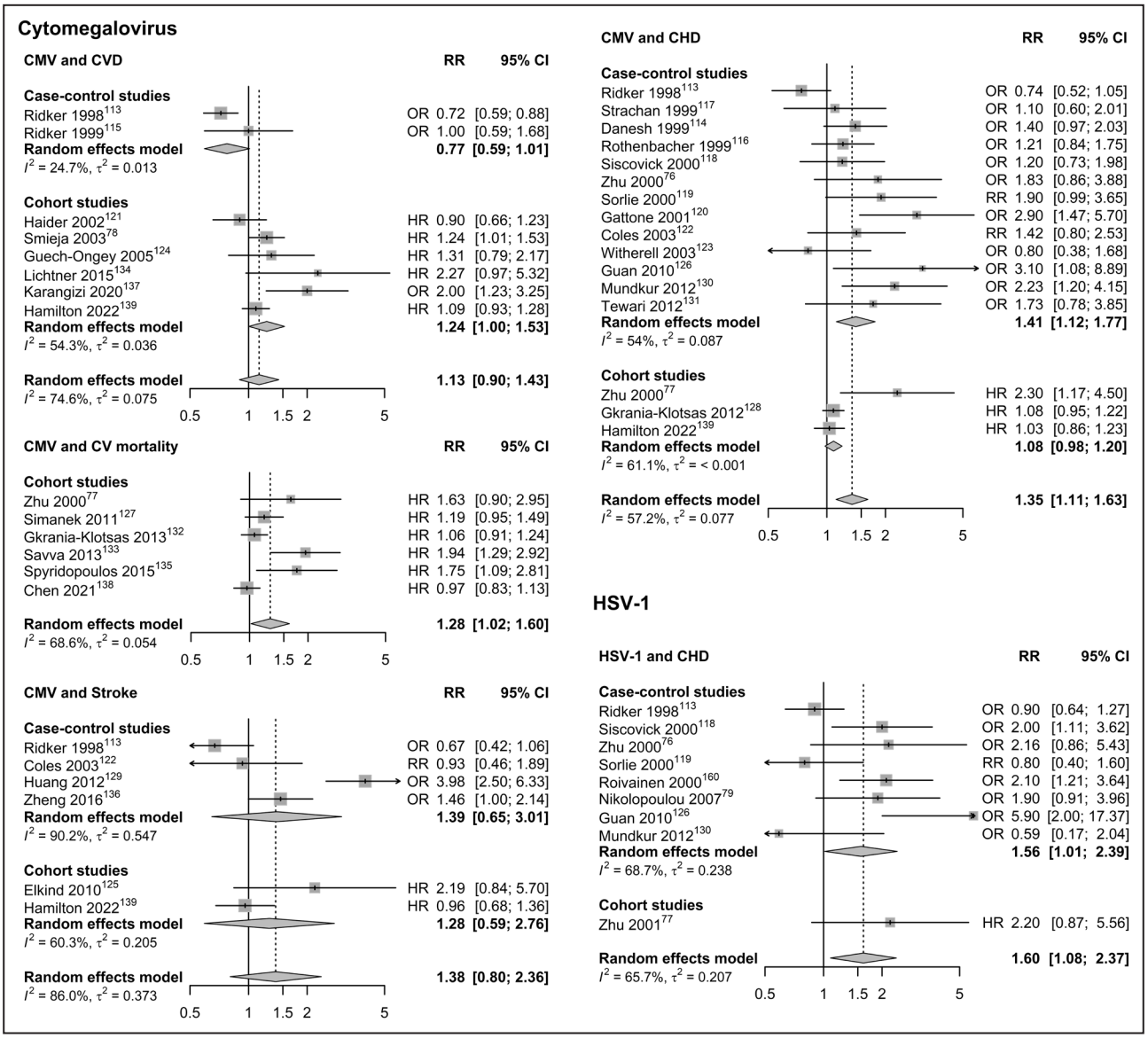

Figure 7. Cytomegalovirus and herpes simplex virus type 1 and the risk of cardiovascular disease.

noncommunicable diseases, especially CVD, increasing, only 2 case–control studies examined the association between HIV infection and CVD, and further investigation is required. Integration of CVD screening and management into HIV care has been shown to be essential and must be scaled up in sub-Saharan Africa.[177,179]

Our study confirmed that HCV increased the risk of CHD, stroke, and CVD death.[10] Persistent elevated risk of CHD was consistently observed in cohort studies with a mean follow-up period of ≥5 years. Direct-acting antiviral therapy has revolutionized the treatment of HCV, achieving sustained virological response rates of >90%.[180,181] Direct-acting antivirals may also reduce the risk of CVD in HCV-infected individuals, although more research may be necessary.[182,183] Screening and treatment of HCV are critical, and further efforts are required to meet the global target for hepatitis elimination.

Herpesvirus infections are highly prevalent, with global seroprevalence estimates ranging from 13% for herpes simplex virus type 2 to 67% for HSV-1, 83% for cytomegalovirus, and >90% for VZV.[184–187] Given the high seroprevalence, the potential adverse effects of latent viral infections have important implications at the population level. Herpes zoster, which results from the reactivation of latent VZV, was associated with a higher risk of stroke and CHD. Elevated risk of CVD persisted for almost 10 years in several large cohort studies. Vaccines against herpes zoster may reduce the risk of cardiovascular events and our study highlights the importance of prevention.[188]

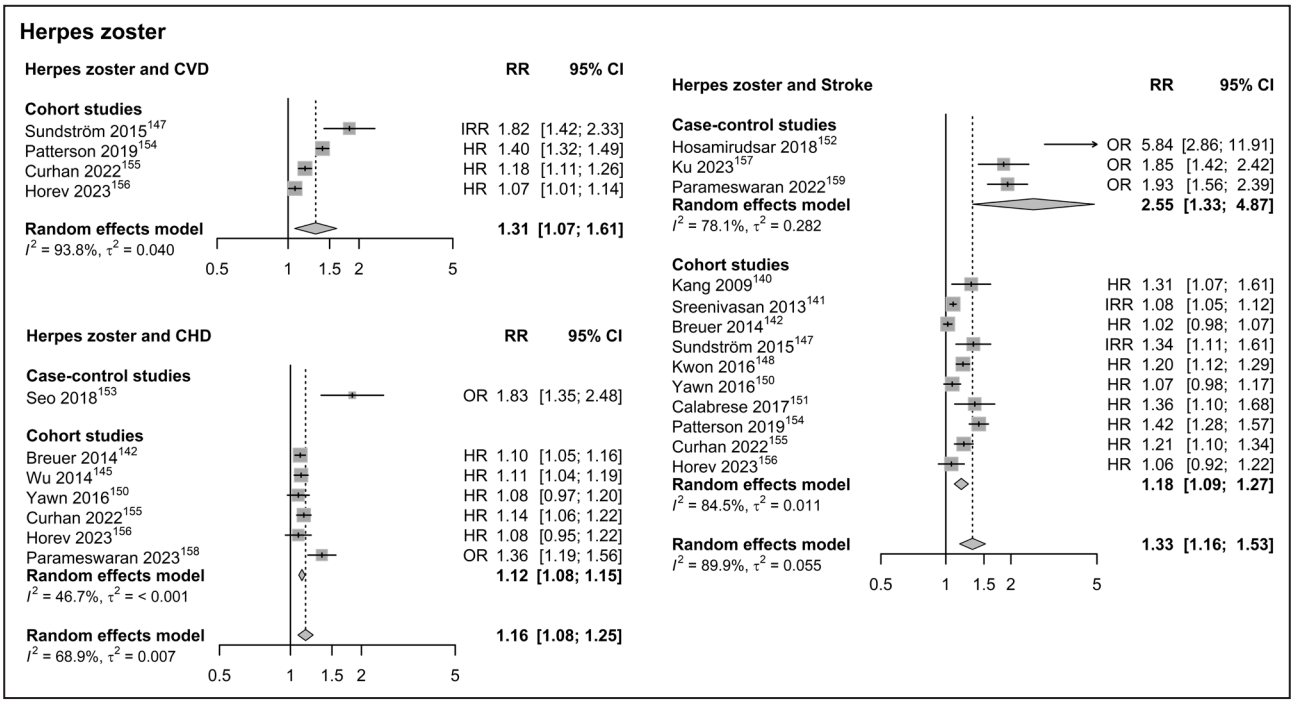

Figure 8. Herpes zoster and the risk of cardiovascular disease.

Cytomegalovirus infection was associated with a higher risk of CVD death; however, there is insufficient evidence to determine the effect of cytomegalovirus on the risk of CHD and stroke. Cytomegalovirus infection was associated with an increased risk of CHD in the meta-analysis of case–control studies; however, recent cohort studies did not confirm the association. Cytomegalovirus reactivation is known to be associated with cardiac allograft rejection and accelerated atherosclerosis in solid organ transplant recipients.[189] Subclinical reactivation of cytomegalovirus may be common over the life course in the general population, and evaluating reactivation or recent infection may be necessary to understand its potential adverse effects. Additionally, our study found the association of HSV-1 seropositivity with an elevated risk of CHD; however, most studies were based on case–control studies, and large cohort studies are needed to confirm these findings.

HPV, dengue, and chikungunya virus infection have been linked to an increased risk of CVD on a limited basis. The estimated global HPV prevalence in women was 12%, with the highest prevalences in Latin America (16%), Eastern Europe (21%), and sub-Saharan Africa (24%).[190] Persistent HPV infection has been associated with elevated systemic levels of proinflammatory cytokines.[191] Moreover, it has been recognized that the inactivation of the tumor suppressor protein p53 by the HPV E6 protein may accelerate atherosclerosis development.[192] Dengue is a growing global health concern. Prior case studies documented that severe dengue causes cardiac involvement, ranging from elevated cardiac biomarkers to ECG abnormalities and severe myocarditis.[193] Chikungunya is another arthropod-borne viral disease, and a large study from Brazil reported an elevated risk of CVD death following chikungunya infection.

Although Latin America, Africa, and South and Southeast Asia face a higher burden of infectious diseases, studies from these regions remain scarce.[194] For example, rates of illness and death from influenza, particularly in older adults, were estimated to be the highest in sub-Saharan Africa and Southeast Asia.[195] The distribution of traditional risk factors for CVD, viral pathogens, and health care access varies across countries. Additionally, multiple viral infections may have cumulative effects on the risk of CVD. Therefore, more research is needed to comprehensively assess the effect of viral infections on the risk of CVD. Furthermore, uptake of the influenza vaccine has been low in most countries, and further efforts are needed to improve global vaccine coverage.

Several limitations of our study are worth noting. We observed moderate to high heterogeneity in effect estimates across most viral infections; therefore, pooled estimates for some findings warrant cautious interpretation. Between-study heterogeneity may have been influenced by variations in study design, country, setting, and patient characteristics, including underlying comorbidities, use of antivirals and other medications, and coinfections. We separated

case–control studies and cohort studies when pooling the estimates and emphasized findings based on cohort studies because most case–control studies were small and tended to overestimate the effect estimates. We used funnel plots to assess publication bias. However, interpreting funnel plots can be challenging, particularly in our meta-analysis, due to between-study heterogeneity, which may have led to asymmetry. Additionally, most cohort studies were large, leaving too few small studies to evaluate potential publication bias. Although most studies adjusted for important cardiovascular risk factors, unmeasured confounding factors such as genetics and coinfections with multiple other viral and bacterial infections may have biased the results. Our study focused on viral infections that affect the general population and did not identify high-risk groups (eg, transplant recipients) that may be affected disproportionately by viral infections. Conducting research during the early COVID-19 pandemic was challenging due to limited testing, difficulties in assessing infection status, and identifying an appropriate comparison group. Thus, misclassification of exposure status may have biased the results of several studies on SARS-CoV-2 infection. This may have also contributed to substantial between-study heterogeneity observed in studies of SARS-CoV-2 infection. Nevertheless, the consistency of findings across SCCS and cohort studies is reassuring.

CONCLUSIONS

Influenza and SARS-CoV-2 infections were associated with an elevated risk of acute MI and stroke. Chronic viral infections, including HIV, hepatitis C virus, and herpes zoster, were associated with a risk of CHD and stroke in long-term cohort studies. Cytomegalovirus, HSV-1, hepatitis A virus, HPV, RSV, dengue, chikungunya, and other viral infections require further research, especially because these viral infections are highly prevalent globally. Our study highlights the importance of integrated preventive measures, especially for adults with traditional risk factors for CVD. Vaccines may play an important role in preventing the risk of CVD.

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Received March 26, 2025; accepted August 15, 2025.

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Acknowledgments

Author contributions: All authors contributed to the study conception. K.K., C.F.M., and J.M.F. performed the literature search, data extraction, and created tables and figures. K.K. conducted the data analysis and wrote the first draft of the manuscript. All authors contributed to the interpretation of the data, critically revised the manuscript, and approved the final version of the manuscript.

Sources of Funding

None.

Disclosures

None.

Supplemental Material

Data S1
Tables S1–S14
Figures S1–S15

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