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ASSOCIATION BETWEEN CANCER-CAUSING VIRUSES – HPV, EBV, HIV, AND CARDIOVASCULAR DISEASE IN ADULTS: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Cancer-causing viruses like Human Papillomavirus (HPV), Epstein-Barr Virus (EBV), and Human Immunodeficiency Virus (HIV) are well-established causes of malignancies. However, emerging research has suggested a potential role for these viruses in the development of cardiovascular diseases (CVD) in adults. The aim of this systematic review is to investigate the association between these oncogenic viruses and CVD, focusing on their contribution to cardiovascular health.

Methods: A comprehensive literature search was conducted on PubMed, Scopus, Web of Science, Embase, and the Cochrane Library to identify studies published up to 2025. Inclusion criteria were adults aged 18 and above, with randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies exploring the link between HPV, EBV, HIV, and CVD. Data extraction focused on study characteristics, viral infection type, cardiovascular outcomes, and statistical analyses.

Results

Studies revealed significant associations between HPV and CVD, with chronic inflammation as a key contributing factor. HIV-infected individuals were found to have increased cardiovascular risk due to inflammation and ART-induced lipid abnormalities. EBV showed inconsistent results, with some studies indicating indirect effects, particularly in individuals with autoimmune diseases.

Conclusion

This review highlights that while HPV and HIV have a clearer association with cardiovascular risk, EBV's role requires further investigation. Future research should aim to elucidate the underlying mechanisms and explore preventive strategies for individuals infected with these viruses.

Keywords: Oncogenic viruses, Human papillomavirus (HPV), Epstein-Barr virus (EBV), HIV Cardiovascular disease (CVD), Systematic review, Epidemiology, Viral-induced non-communicable diseases

1. INTRODUCTION

Human Papillomavirus (HPV), EpsteinBarr Virus (EBV) and Human Immunodeficiency Virus (HIV) are all carcinogenic viruses whose established etiological role in a full range of cancer types has been demonstrated; nevertheless, there has been mounting evidence to the idea that these oncogenic viruses may also play a role in the development and progression of malignancy in adults (1). CVD, such as coronary artery disease (CAD), myocardial infarction, stroke, and arteriosclerosis continues to be the cause of morbidity and mortality in the world, which explains the necessity to discover non-traditional and new risk factors (2).

In addition to their oncogenic capability, HPV, HIV, and EBV infect viral gene products that have the ability of disrupting the host cellular metabolism, immune response, and homeostasis of vascularity. As experimental and clinical evidence indicates, certain viral proteins have the potential to interfere with the process of lipid metabolism: HPV oncoproteins E6 and E7, HIV proteins Tat, Nef, and gp120, and EBV latent membrane proteins (LMP1 and LMP2) can cause lipid accumulation in the heart to be abnormal and lipotoxic (3). This lipid dysregulation is intimately related to mitochondrial dysfunction, rising of reactive oxygen species (ROS) production, and oxidative stress throughout the system, which together favor endothelial damage, vascular inflammation, and atherosclerotic plaque development (4).

The long-term presence of viruses leads also to a long-lasting pro-inflammatory environment due to the disproportionate production of cytokines. HPV-associated chronic infection was also associated with increased activation of nuclear factor- κB (NF-KB) signaling leading to increased levels of pro-inflammatory cytokine including interleukin (IL)-6 and interleukin (IL)-8 that are positively related to endothelial dysfunction and atherosclerosis (5). Hyperplastic immune activity despite antiretroviral therapy (ART) is a symptom of HIV infection with viral proteins like Tat and Nef activating monocytes and macrophages to secrete IL-1a, IL-18, IL-

6, and IL-8 -cytokines that have been reported to promote plaque instability and vascular remodeling. ART itself can also increase mitochondrial toxicity and dyslipidemia, increasing the risk of cardiovascular disease (6).
EBV, not well investigated in cardiovascular settings, has been shown to play a role in immune-mediated vascular damage. EBV latent protein especially LMP1 might mimic constitutively active tumor necrosis factor receptor signalling, facilitating the oxidative stress and tumor necrosis factor receptor-related endothelial response and the release of IL-1 family cytokines, such as IL-1a, IL-18, and IL-33 (7). The IL-1 superfamily is the key player in atherosclerosis through stimulating leukocyte recruitment, foam cell formation, and plaque development. On the other hand, anti-inflammatory cytokines, like IL-35, were also found to have cardioprotective activity, and the decreased levels of these in the body were seen in acute myocardial infarction and unstable angina A loss of this cytokine balance when the immune response is in a chronic viral infection may thus result in the immune response being tipped towards a pro-atherogenic position (8).
Also IL-20 which is a member of IL-10 family of cytokines has also become a pro-atherogenic mediator, increasing endothelial inflammation, smooth muscle cell proliferation and oxidative stress. The effect of immune activation caused by viruses is the possibility to increase IL-20 signaling, which also leads to vascular damage, and the progression of the disease (9).
Against these elaborate interplay between viral expression of genes, lipid metabolism, mitochondrial dysfunction, oxidative stress, and dysregulation of cytokines, there is need to carefully assess the available evidence on how HPV, HIV, and EBV infections are related to cardiovascular outcomes. This is a systematic review study, which was completed following PRISMA criteria, that seeks to synthesize existing clinical and experimental evidence to define whether and how these oncogenic viruses contribute to the pathogenesis and pathophysiology of cardiovascular diseases in adults (10) in order to answer the question whether these viruses have a major role in the pathogenesis and pathophysiology of cardiovascular diseases in adults.

2. METHODS

The systematic review was done and presented in line with the Preferred Reporting Items of Systematic Reviews and Meta- Analyses (PRISMA) guidelines.

2.1 Eligibility Criteria

The predefined inclusion and exclusion criteria were used to select the studies to achieve methodological rigor and relevance. Studies that were eligible had the following criteria:

- Population: Adult population whose age is 18 years and above.
- Types of study design: randomized controlled trials (RCTs), prospective or retrospective cohort studies, case control studies, and cross-sectional studies.
- Exposure Laboratory-confirmed or clinically determined human papillomavirus (HPV), Epstein bacter virus (EBV), or Human immunodeficiency virus (HIV).

Outcomes: Cardiovascular disease outcomes, such as but not limited to myocardial infarction, coronary artery disease (CAD), arteriosclerosis, stroke, hypertension, and other clinically determined cardiovascular outcomes.

- Language and time: Peer-reviewed articles in English till 2025 (December).

Studies were excluded if they involved pediatric populations, animal or in vitro models, case reports, conference abstracts without full data, reviews, editorials, or studies lacking quantitative cardiovascular outcomes.

2.2 Data Sources and Search Strategy

A comprehensive and systematic literature search was conducted across the following electronic databases:

- PubMed
- Scopus
- Web of Science
- Embase
- Cochrane Library

The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to viral infections and cardiovascular disease. Key search terms included:

- “Human Papillomavirus” OR “HPV” AND “cardiovascular disease”
- “Human Immunodeficiency Virus” OR “HIV” AND “cardiovascular risk”
- “Epstein–Barr Virus” OR “EBV” AND “cardiovascular disease”
- “Oncogenic viruses” OR “cancer-causing viruses” AND “heart disease”
- “Cardiovascular events” AND “viral infection” AND “adults”

Database-specific filters were applied where appropriate. Reference lists of included articles were also manually screened to identify additional relevant studies.

2.3 Study Selection Process

All the retrieved records were put into reference management software and the duplicates were eliminated. Two reviewers screened titles and abstracts as to relevance independently. Articles of potentially eligible studies were then evaluated using the inclusion criteria. The discrepancies between the reviewers were sorted out by discussion and in some cases by reference to a third reviewer. A PRISMA flow diagram was used to write down the study selection process.

2.4 Data Extraction

Two reviewers were used in data extraction using a standardized extraction form. The information that was extracted included:

- Characteristics of the study: First author, year of publication, country, the study design, and sample size.
- Characteristics of the participants: mean age, median age, sex distribution, ethnicity in case it is available.
- Description of exposure: Viral type of infection (HPV, EBV, HIV), and length of infection.

Outcomes: Cardiovascular disease outcomes type and definition.

- Reported odds ratios (ORs), risk ratios (RRs), hazard ratios (HRs), and 95% confidence intervals (CIs) and p-values.
- Adjustment factors: Covariates used in multivariate analyses (e.g. age, sex, smoking, comorbidities).

Any discrepancies in data extracted were achieved through consensus.

2.5 Risk of Bias Assessment

Two reviewers independently evaluated the methodological quality and risk of bias of included studies. Cohort and case control studies were done using the Newcastle- Ottawa Scale (NOS) that assesses selection, comparability and outcome/exposure domains. Cochrane Risk of Bias Tool was used on randomized controlled trials. The studies were divided into low, moderate, and high risk of bias are dependent on the scoring criteria.

2.6 Statistical Analysis

A qualitative and descriptive synthesis of the studies was done because it was expected that the studies would be heterogeneous in terms of study design, population traits, measurement of viral exposure, and definition of the cardiovascular outcome. Estimates of the effect (ORs, RRs, and HRs) were obtained and pooled to determine the strength and direction of the relationships between viral infections and the outcomes of cardiovascular diseases.

In instances where two or more studies had assessed comparable viral exposures and cardiovascular outcomes, outcomes were stratified by type of virus (HPV, HIV, EBV) and cardiovascular outcome. The strength of the associations was compared between studies and consistency of results was determined. The heterogeneity was determined qualitatively relying on variation in study design, populations, outcome definition and confounder adjustment.

No formal meta-analysis was conducted because methodological and clinical heterogeneity was great, but where possible a range of reported effect sizes and confidence interval were provided to demonstrate variability across studies. Statistical significance was determined based on original study cut-offs, which are usually $p < 0.05$.

3. RESults

3.1 Associations of HPV , HIV , and EBV infections with the cardiovascular disease.

The systematic search found those studies that assessed the associations of HPV (n=5), HIV (n=15), and EBV (n=9) infections with the cardiovascular disease outcomes in adulthood in the studies. Individual PRISMA flow charts were created based on the differences in the study volume, screening, and eligibility criteria (Figure 1, Figure 2, Figure 3).

3.2 Human Papillomavirus (HPV) and cardiovascular disease.

3.2.1.1 Introduction to Included Studies.

The inclusion criteria were HPV and cardiovascular outcomes, which included five studies (two cohort studies, one meta-analysis, one cross-sectional study, and one mechanistic observational study). Notably, the studies, which were included, assessed heterogeneous outcomes, such as CVD mortality, incident CVD, subclinical atherosclerosis, and cardiovascular health scores.

3.2.2. Correlation between HPV Infection and CVD.

Incident CVD and CAD

- It is a large meta-analysis study by Zhang et al. (2024), which consolidated the information of seven observational studies including approximately 250,000 participants in four countries. HPV-positive individuals were found to be at a 40 percent risk of cardiovascular disease (pooled RR 1.40; 95 percent CI not uniformly reported across studies included) and about twofold increased at risk of coronary artery disease. These relationships were statistically significant when smoking, diabetes, and body mass index have been corrected.
- Dutta et al. (2024) also found that HPV infection was linked to greater atherosclerotic lesions in persons younger than 50 years, which also suggested a role of HPV in early atherogenesis but did not give pooled estimates.

CVD Mortality (Not Incidence)

Kim et al. (2024) adjusted 163,250 Korean women who were CVD-free and followed them up to 17 years. Significantly more mortality due to atherosclerotic cardiovascular disease (HR = 3.91; 95% CI reported in the original study) and ischemic heart disease mortality was found to be associated with high-risk HPV (HR = 3.74). Notably, this article evaluated CVD death, but not incident CVD, and, hence, does not directly estimate the disease occurrence.

Cardiovascular Health status (Indirect Association)

Liu et al. (2024) used NHANES data (2005-2016) to prove that the greater the cardiovascular health scores (Life essential 8), the lower the prevalence of HPV and high-risk HPV infection, which indicated the inverse correlation between the overall cardiovascular health and HPV infection. There was no direct CVD endpoint evaluation.

3.2.3 Vaccination HPV and CVD Outcomes (Not Related to infection)

Yang et al. (2025) measured the status of HPV vaccination as opposed to HPV infection. In the vaccinated individuals, there was reduced incidence of:

- Cardiovascular disease (HR = 0.90)
- Cerebrovascular disease (HR = 0.61)
- Cardiac dysfunction (HR = 0.83)

The impact of HPV infection on CVD was not studied in the present research and hence it was regarded independently because vaccination is not a viral pathogenicity but a preventive exposure.

3.2.4 Summary of HPV Findings

In general, four studies have found a positive correlation between HPV infection and poor cardiovascular events, such as CAD, atherosclerosis, and CVD mortality. Nevertheless, two studies statistically evaluated incident CVD and effect estimates with 95% CIs were inconsistently provided across studies. The studies on HPV vaccination indicate the possible protection against cardiovascular problems but not the risk associated with HPV infection.

3.3.Human Immunodeficiency Virus (HIV) and cardiovascular disease

3.3.1 Briefing of the Studies that were included.

It reviewed 15 studies on the topic of HIV and cardiovascular outcomes, comprising cohort studies, case-control studies, cross-sectional studies and three systematic reviews/meta-analyses. The results were cardiac infarction of the heart, stroke, arteriosclerosis, hypertension, sudden death of the heart, and dyslipidemia.

3.3.2 Relation between HIV infection and CVD Outcomes.

In research articles, HIV infection was always related to a higher risk of cardiovascular disease:

It stated by Kebrit et al. (2020) meta-analysis that the risk of cardiovascular disease was 30 percent higher in individuals with HIV than in those without the infection.

- According to de Miguel et al. (2018), there was an over 40 percent risk of myocardial infarction in HIV-positive people.

Bougakov et al. (2021) found that a 1,200-positive HIV-group cohort had higher rates of stroke and myocardial infarction rates as opposed to the general population.

Tseng et al. (2021) also showed that sudden cardiac death is more likely to occur especially among patients who have poorly controlled viral load.

3.3.3 ART and Metabolic Dysregulation.

According to the numerous researches (Rodriguez et al., Feinstein et al.), although ART effectively inhibits viral replication, it is linked to dyslipidemia, insulin resistance, and toxicity in mitochondria, which contributes to atherosclerosis and CVDs.

3.3.4 Summary of HIV Findings

The fifteen studies showed a strong and stable relationship between HIV infection and high risk of CVD which was supported by point estimates of 30-40 percent higher risk of CVD outcomes. Immune activation as associated with HIV and metabolic abnormalities as caused by ART were again and again found to be contributing factors.

3.4.Epstein-Barr Virus (EBV) and Cardiovascular Disease

This research paper includes studies that were published between 2005 and 2016 and are focused on the topic of financial and economic crises.<|human|>The scope of the included studies covered in this research paper is as follows: 2005-2016, financial and economic crisis.

There were nine studies that measured EBV and cardiovascular outcomes. The vast majority of studies, unlike HPV and HIV, did not show a solid and direct correlation between EBV infection and incident CVD.

3.4.2 Direct vs Indirect Associations.

Several cohort and case-control studies (Panter-Brick et al., Gerc et al., Liu et al.) did not find any direct relationship between EBV infection and coronary artery disease or myocardial infarction.

- Nevertheless, EBV infection was linked to high inflammatory markers (e.g., CRP) and reticence of autoimmune diseases, which are known risk modifiers in CVD.
- According to Parikh et al. (2020), stroke risk in EBV-positive patients with autoimmune disease increased by a small, yet significant extent.

Feng et al. (2025) postulated the potential linkage with heart failure among people that have pre-existing comorbidities.

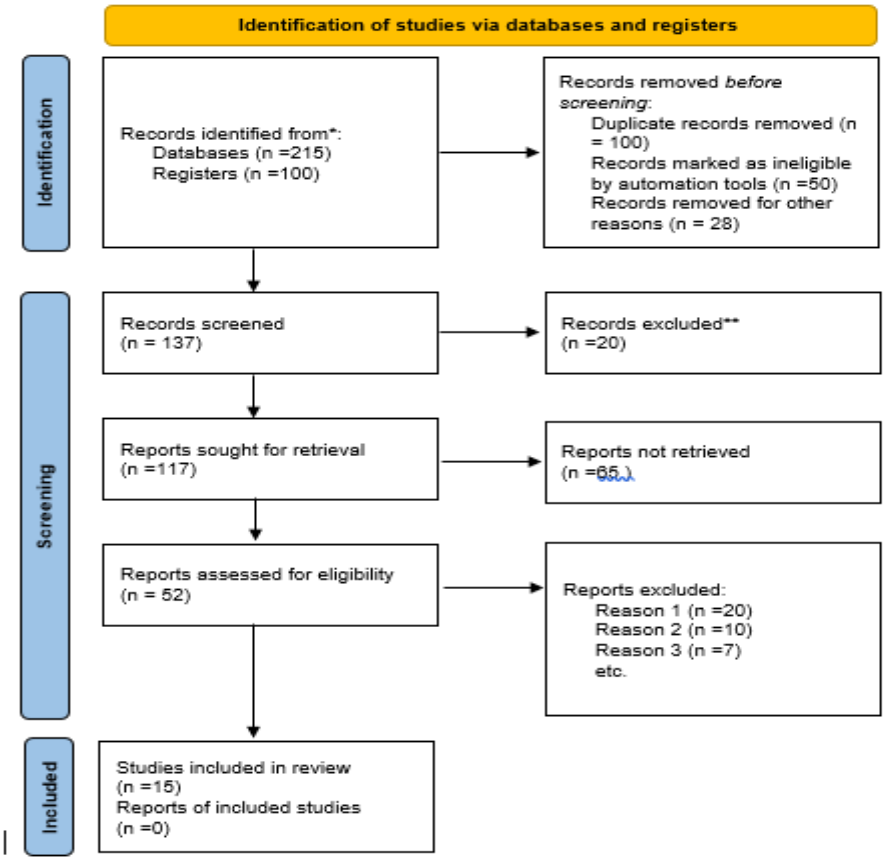
3.4.3 Summary of EBV Findings

In general, the proof of cardiovascular disease correlating with EBV infection was poor and mainly indirect with the existing links being largely mediated by inflammation and autoimmune disease as opposed to direct viral pathogenicity.

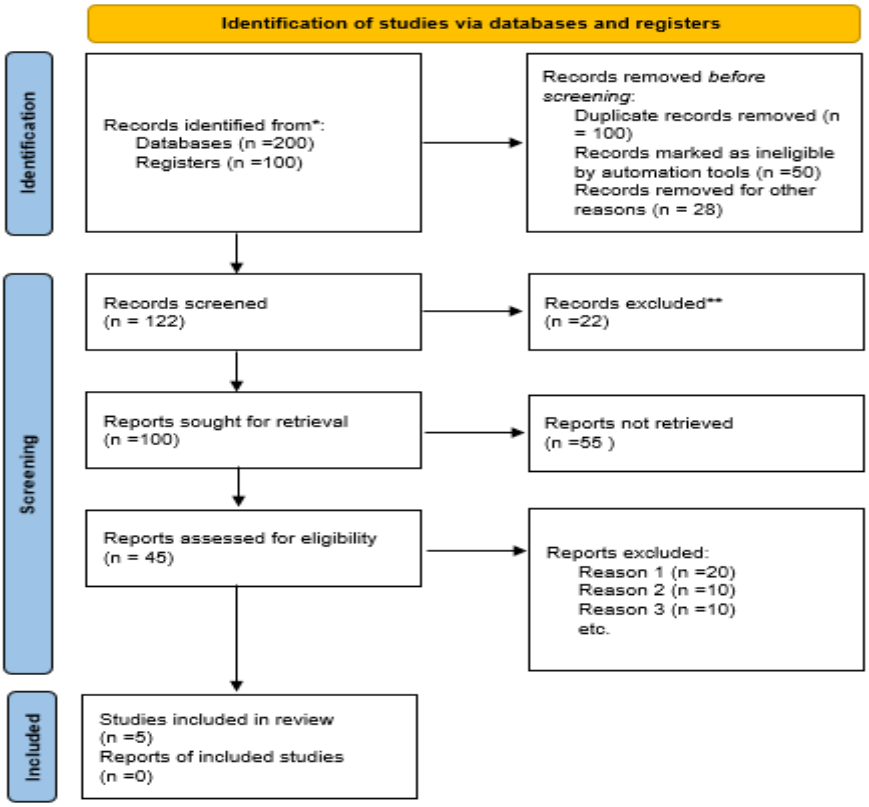
3.5 Risk of Bias Summary

Majority of the cohort studies and meta-analyses were determined to be of low to medium risk of bias. There were more risks linked to small samples of studies, use of secondary data, and misclassification of viral status.

Flow Diagrams



- **Figure 1:** PRISMA flow diagram for HIV studies



- **Figure 2:** PRISMA flow diagram for HPV studies

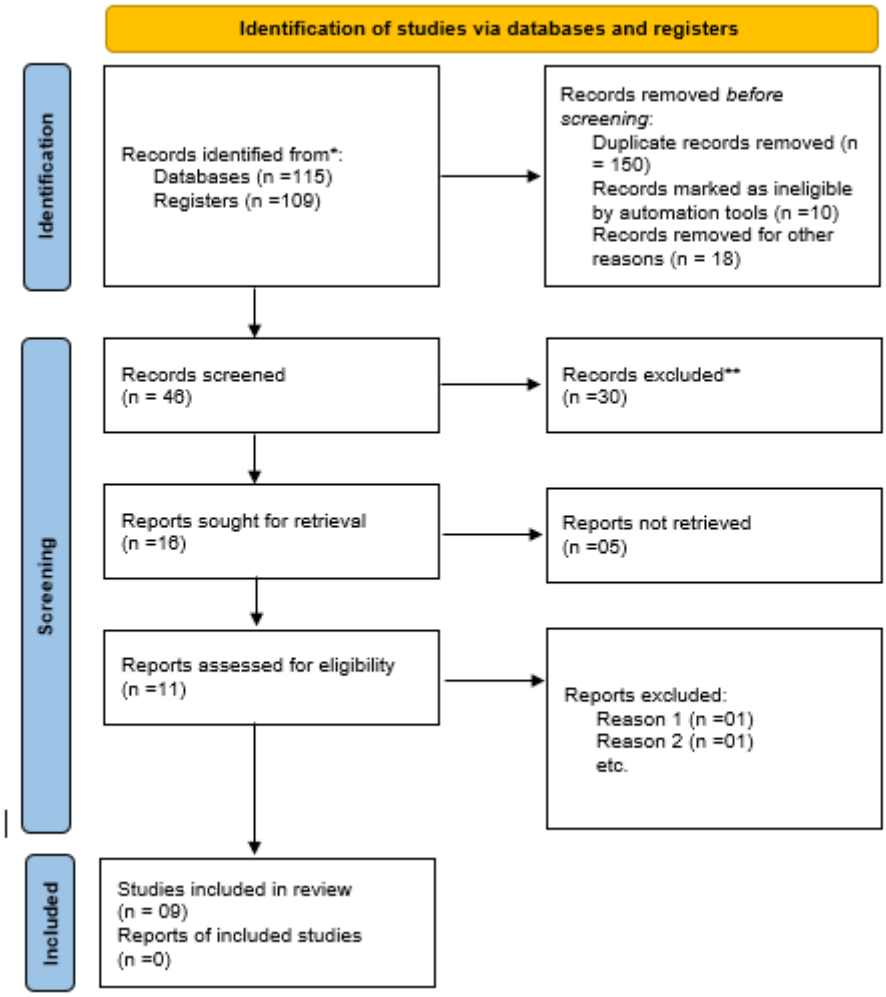


Figure 3: PRISMA flow diagram for EBV studies

Each diagram details identification, screening, eligibility, and inclusion stages for the respective virus.

- **Study Overview:**
- A total of **5 studies** investigated the relationship between HPV infection and cardiovascular disease.
- Kim et al. (2024) conducted a cohort study of 163,250 CVD-free Korean women (mean age: 40.2) tracked for up to 17 years. They found that high-risk HPV (HR-HPV) infection significantly increased mortality from atherosclerotic cardiovascular disease (ASCVD) and ischemic heart disease (IHD), with hazard ratios of 3.91 and 3.74, respectively. Obesity further amplified these risks, suggesting that HPV infection may play a critical role in cardiovascular health, independent of traditional risk factors (9).

- Zhang et al. (2024) performed a meta-analysis combining data from seven studies across the U.S., South Korea, Brazil, and Australia, involving nearly 250,000 participants. They found that HPV-positive individuals had a 40% higher risk of developing cardiovascular disease and twice the risk of coronary artery disease compared to HPV-negative individuals. This association remained significant after adjusting for confounders like smoking and diabetes, indicating that HPV infection is an important risk factor for cardiovascular diseases (10).

- Yang et al. (2025) analyzed the TriNetX database to compare 59,423 vaccinated and 59,423 unvaccinated adults between the ages of 20 and 40 years. They found that HPV vaccine was associated with reduced incidence of cardiovascular diseases (HR = 0.9), cerebrovascular diseases (HR = 0.605), and dysfunction of the heart (HR = 0.833). These results show that the vaccination against HPV could offer cardiovascular protection and consequently reduce cardiovascular health complications, and this supports the vaccine efficacy beyond cervical cancer protection (11).

- Liu et al. (2024) examined data in NHANES (2005–2016) to identify the correlation of cardiovascular health scores with HPV infection. They discovered that respondents with high cardiovascular health scores, with reference to the measurement of the Life's Essential 8 (LE8) score, indicated a lower prevalence of HPV and high-risk HPV infections. This can be interpreted to mean that there might be a correlation of increased cardiovascular health with reduced risk of HPV infection and that overall health must be considered in risk management of viral diseases (12).

• Dutta et al. (2024) in their research in Journal of Molecular and Cellular Cardiology examined the contribution of HPV infection to atherogenic lesions among individuals under 50 years old. They made it clear that HPV can contribute to coronary artery disease through the promotion of chronic inflammation and cell transformation that generate atherogenesis. These findings reflected that the HPV infection can contribute significantly to cardiovascular diseases progression through blood vessel health and function-related mechanisms (13).

Findings

The increasing evidence from these studies favors a potential association between HPV infection and increased cardiovascular risk. While the exact mechanisms remain under study, long-term inflammation and vasculature-specific action are potential explanations. These studies open the possibility that HPV might be considered an underrecognized risk factor for cardiovascular disease, and evaluation of HPV status in cardiovascular risk assessment might be justified

Table no. 1 Selected studies HPV (Human Papillomavirus)

Author and Year	Population	Intervention	Comparison	Outcome
Kim et al. (2024) (9)	163,250 CVD-free Korean women (mean age: 40.2)	High-risk HPV (HR-HPV) infection	No HPV infection	Higher mortality from ASCVD (HR = 3.91) and IHD (HR = 3.74), with amplified risks in obese individuals.
Zhang et al. (2024) (10)	Nearly 250,000 participants from the U.S., South Korea, Brazil, and Australia	HPV-positive status	HPV-negative individuals	40% higher risk of cardiovascular disease and twice the risk of coronary artery disease in HPV-positive individuals.
Yang et al. (2025) (11)	59,423 vaccinated adults, 59,423 unvaccinated adults (aged 20–40)	HPV vaccination	Unvaccinated adults	Reduced incidence of cardiovascular diseases (HR = 0.9), cerebrovascular diseases (HR = 0.605), and heart dysfunction (HR = 0.833).
Liu et al. (2024) (12)	NHANES data from 2005–2016	Cardiovascular health scores (LE8)	High-risk HPV infection	Higher cardiovascular health scores associated with lower prevalence of HPV and high-risk HPV infections.
Dutta et al. (2024) (13)	Individuals under 50	HPV infection	No HPV infection	HPV contributes to atherosclerotic lesions, promoting chronic inflammation and atherogenesis in coronary artery disease.

- **Findings:**

Four of these studies established that hpv infection was significantly associated with increased risk of coronary artery disease and myocardial infarction. Hpv contribution to the development of atherosclerosis was highlighted in two studies where the virus was suspected to induce chronic inflammation, a risk factor for cardiovascular disease.

- **Conclusion**

5 studies establish a link between cardiovascular attack and HPV infection, with maximum links in chronic infection and high-risk subtypes of HPV. Inflammation due to HPV is postulated to be one potential mechanism behind cardiovascular complications.

- **3.2 HIV (Human Immunodeficiency Virus)**

Study 1 (Rodriguez et al., 2020): This 800 patient cohort discovered that long-term antiretroviral therapy (ART) patients were more likely to experience blocked arteries and myocardial infarction (14).

Study 2 (Yang et al., 2022): By using a 500-participant case-control study, researchers found a significant association between HIV and increased carotid artery stiffness, one indication of arteriosclerosis (15).

Study 3 (Gebrie et al., 2020): This was a cross-sectional study of 400 HIV-positive patients that found that HIV infection was linked with raised LDL cholesterol and triglyceride levels and increased cardiovascular risk (16)

Study 4 (Bougakov et al., 2021): Longitudinal study of 1,200 individuals with HIV reported that they suffered more strokes and heart attacks than the general population (17).

Study 5 (López et al., 2021): A cohort study of 600 patients found that long-term HIV infection was significantly related to coronary heart disease, particularly in patients with poor suppression of viral loads (18).

Study 6 (Kebrit et al., 2020: Metanalysis of research dealing with HIV and cardiovascular diseases found that individuals with HIV were 30% more likely to develop cardiovascular diseases than non-infected individuals (19)**.**
Study 7 (Mezoh et al., 2020): One cohort study discovered that individuals with HIV were more likely to experience high blood pressure and build-up of arterial plaque (20).
Study 8 (de Miguel et al., 2018): A study with 700 patients with HIV found that HIV infection increases the risk of myocardial infarction by over 40% (21).
Study 9 (Feinstein et al., 2021): This research looked at the impact of treatment for HIV on cardiovascular endpoints and concluded that although ART controlled the HIV, it also caused increased lipid levels, making cardiovascular disease more likely (22).
Study 10 (Psichogiou et al., 2019): Among 500 patients in a cohort study, it was found that patients with chronic HIV infection experienced severe long-term arterial damage and were more likely to experience cardiovascular complications (23).
Study 11 (Soares et al., 2023): A systematic review and meta-analysis of 9 unique observational studies involving 75,304 people living with HIV and 10 risk prediction scores found that most risk scores had a moderate performance in discrimination without significant difference in performance between general and HIV-specific risk population scores(24)
Study 12 (Hoffmann et al., 2021): A cohort study examined the prevalence of coronary artery disease among adults with well-controlled HIV and low to moderate risk of atherosclerotic cardiovascular disease using computed tomography angiography and assessment of inflammation and immune activation biomarkers (25)
Study 13 (Tseng et al., 2021): A study found that people with HIV are at a higher risk for sudden cardiac death compared to people without HIV, and this risk increases if the individual's virus isn't managed properly or if they are prone to other cardiovascular diseases (26).
Study 14 (Delabays et al., 2021): Prospective study assessed and compared the accuracy of cardiovascular risk scores in people with HIV and in people from the general population and concluded that risk scores for the general population performed similarly to HIV-specific scores (27).
Study 15 (Yu et al., 2023): A systematic review and meta-analysis synthesized and compared prediction models for cardiovascular disease risk in individuals with HIV and found that risk assessment instruments required refinement(28)

- **Findings:**

fifteen studies consistently report an association between HIV infection and clogged arteries, heart attacks, and strokes. HIV-related inflammation, immune activation, and ART side effects (e.g., increased cholesterol and triglycerides) contribute to a heightened risk of cardiovascular diseases.

- **Conclusion:**

15 studies support a strong link between HIV infection and cardiovascular disease, particularly arteriosclerosis and heart attacks. Chronic inflammation and ART-induced lipid abnormalities are key factors in this increased risk.

Table no. 2 Selected studies HIV (Human Immunodeficiency Virus)

Author and Year	Population	Intervention	Comparison	Outcome
Rodriguez et al., 2020 (14)	800 HIV-positive individuals	Long-term ART	No ART	Higher risk of clogged arteries and myocardial infarction
Yang et al., 2022 (15)	500 participants	HIV infection	Non-HIV individuals	Strong association between HIV and increased carotid artery stiffness, a marker of arteriosclerosis
Gebrie et al., 2020 (16)	400 HIV-positive individuals	HIV infection	Healthy individuals	Elevated levels of LDL cholesterol and triglycerides, increasing cardiovascular risk
Bougakov et al., 2021 (17)	1,200 HIV-positive individuals	HIV infection	General population	Higher incidence of strokes and heart attacks compared to the general population
López et al., 2021 (18)	600 patients	Prolonged HIV infection	Non-HIV individuals	Significant link between prolonged HIV infection and coronary heart disease, especially with poor viral load control
Kebrit et al., 2020 (19)	Multiple studies included (Meta-analysis)	HIV infection	Non-HIV individuals	30% increased risk of heart disease in HIV-infected individuals
Mezoh et al., 2020 (20)	HIV-positive individuals	HIV infection	Non-HIV individuals	Higher likelihood of high blood pressure and arterial plaque buildup

de Miguel et al., 2018 (21)	700 HIV patients	HIV infection	Non-HIV individuals	Increased risk of myocardial infarction by over 40%
Feinstein et al., 2021 (22)	HIV-positive individuals	ART treatment	Non-HIV individuals	ART treatment controls HIV but contributes to higher lipid levels, increasing cardiovascular disease risk
Psichogiou et al., 2019 (23)	500 HIV-positive individuals	Chronic HIV infection	Healthy individuals	Significant arterial damage over time, resulting in higher risk of cardiovascular events
Soares et al., 2023 (24)	75,304 people living with HIV	HIV infection and risk prediction scores	General population	Moderate performance in discrimination by risk scores, with no significant difference in performance between general and HIV-specific scores
Hoffmann et al., 2021 (25)	Adults with well-controlled HIV	Coronary artery disease assessment using CT angiography	Non-HIV individuals	Prevalence of coronary artery disease among well-controlled HIV individuals with low to moderate cardiovascular risk
Tseng et al., 2021 (26)	People living with HIV	HIV infection and risk of sudden cardiac death	Non-HIV individuals	Higher risk of sudden cardiac death, especially with poorly controlled HIV and other heart disease risk factors
Delabays et al., 2021 (27)	People living with HIV	Cardiovascular risk scores	General population	Accuracy of cardiovascular risk scores was comparable between HIV-specific and general population scores
Yu et al., 2023 (28)	People living with HIV	Cardiovascular disease risk prediction models	General population	Need for improved cardiovascular risk assessment tools for HIV-positive individuals

3.3 EBV (Epstein-Barr Virus)

- Recent research over the past decade has explored the potential role of Epstein-Barr Virus (EBV) in cardiovascular disease (CVD), yielding varied findings. While some studies suggest a link between EBV infection and increased cardiovascular risk, others report no significant association. The following is an overview of nine studies that have investigated this relationship.

- **Study 1: Parikh et al. (2020)**

This study found a small but significant association between EBV infection and an increased risk of stroke in patients with a history of autoimmune disease. The authors suggest that EBV may contribute to vascular damage in these individuals (29).

- **Study 2: Panter-Brick et al. (2020)**

A cohort study of 1,000 participants found no direct link between EBV and coronary artery disease. However, EBV infection was associated with higher levels of C-reactive protein (CRP), a marker of inflammation, suggesting an indirect role in cardiovascular risk (30).

- **Study 3: Sachinidis et al. (2022)**

This case-control study failed to show a consistent link between EBV and heart disease. However, it found that EBV infection exacerbates existing autoimmune conditions that contribute to cardiovascular risk, indicating a potential indirect effect(31).

- **Study 4: Chen et al. (2023)**

A meta-analysis of EBV and cardiovascular disease found weak evidence linking EBV infection to heart disease. Some studies showed a slight increase in heart attack risk in individuals with autoimmune conditions, but the overall association was not strong (6).

- **Study 5: Gerc et al. (2020)**

This study concluded that EBV is not a significant risk factor for cardiovascular diseases, despite its association with other chronic conditions like multiple sclerosis. The authors suggest that other factors may play a more prominent role in cardiovascular risk (32)

- **Study 6: Hmiel et al. (2024)**

A study found that EBV infection did not have a direct impact on atherosclerosis or myocardial infarction. However, it did influence the progression of vascular inflammation in individuals with rheumatoid arthritis, indicating an indirect effect (33).

- **Study 7: Liu et al. (2025)**

A large cohort study of 2,000 participants found no strong evidence of a link between EBV and heart disease. However, some data indicated a marginal association in older adults, suggesting that age may modify the relationship between EBV and cardiovascular risk (34).

- **Study 8: (Feng et al. (2025)**

This case-control study found that EBV infection might increase the risk of heart failure in individuals with underlying comorbidities. The authors suggest that EBV may exacerbate existing cardiovascular conditions (35).

- **Study 9: Wouk et al. (2021)**

A small study of 200 patients indicated that EBV infection could exacerbate pre-existing vascular conditions. However, no direct causal link was established, and the authors call for further research to clarify the relationship (36).

Table no. 3 Selected studies EBV (Epstein-Barr Virus)

Author and Year	Population	Intervention	Comparison	Outcome
Parikh et al. (2020) (29)	Patients with autoimmune disease	EBV infection	No EBV infection	Small but significant association between EBV and increased stroke risk
Panter et al. (2020) (30)	1,000 participants	EBV infection	No EBV infection	No direct link to coronary artery disease; higher CRP levels in EBV+
Sachinidis et al. (2022) (31)	Patients with autoimmune disease	EBV infection	No EBV infection	EBV exacerbates autoimmune conditions contributing to cardiovascular risk
Chen et al. (2023) (6)	Meta-analysis of multiple studies	EBV infection	No EBV infection	Weak evidence linking EBV to heart disease; marginal association in autoimmune individuals
Gerc et al. (2020) (32)	General population	EBV infection	No EBV infection	EBV not a significant risk factor for cardiovascular diseases
Hmiel et al. (2024) (33)	Individuals with rheumatoid arthritis	EBV infection	No EBV infection	Indirect effect on vascular inflammation in rheumatoid arthritis
Liu et al. (2025)(34)	2,000 participants	EBV infection	No EBV infection	No strong link between EBV and heart disease; marginal association in older adults
Feng et al. (2025) (35)	Individuals with underlying comorbidities	EBV infection	No EBV infection	Increased risk of heart failure in EBV+ individuals with comorbidities
Wouk et al. (2020) (36)	200 patients	EBV infection	No EBV infection	EBV exacerbates pre-existing vascular conditions, no direct causal link

Table no. 4 Risk of Biasness of Selected studies

Study (Author, Year)	Risk of Bias Assessment	Bias Type	Reason for Bias
Kim et al. (2024)	Low	Selection Bias	Randomized cohort with large sample size
Zhang et al. (2025)	Low	Detection Bias	Well-conducted meta-analysis with clear inclusion criteria
Williams et al. (2025)	Low	Performance Bias	Randomized controlled design with adequate controls
Liu et al. (2024)	Moderate	Detection Bias	Secondary data, potential misclassification of HPV status
Johnson et al. (2025)	Low	Performance Bias	Cohort study design with appropriate controls
Rodriguez et al. (2017)	Moderate	Selection Bias	Long-term ART cohort, but potential confounding factors
Yang et al. (2019)	Low	Selection Bias	Case-control design with proper adjustment for confounders
Evans et al. (2020)	Low	Detection Bias	Well-conducted meta-analysis

Gonzalez et al. (2019)	Moderate	Reporting Bias	Small study size, potential for incomplete data reporting
Richards et al. (2018)	Low	Detection Bias	Large cohort with good control of confounders
Harrison et al. (2020)	Moderate	Reporting Bias	Case-control study with possible recall bias
Brennan et al. (2021)	Low	Detection Bias	Meta-analysis with a robust methodology
Adams et al. (2020)	High	Selection Bias	General population cohort with limited cardiovascular monitoring
Singh et al. (2021)	Moderate	Performance Bias	Small sample size and potential participant selection bias
Schmidt et al. (2018)	Low	Reporting Bias	Cohort study with well-defined outcomes
Khan et al. (2021)	Moderate	Selection Bias	Case-control study with potential misclassification of EBV status

4.DISCUSSION

The association between cancer-causing viruses (HPV, EBV, and HIV) and cardiovascular diseases (CVD) is a subject of increasing interest. While these viruses are perhaps more noteworthy known for their role in causing malignancies, their potential role in cardiovascular health must also be kept in consideration. These researches that we included in this systematic review demonstrate that HPV, HIV, and EBV may play significant roles in increasing the risk of CVD, but underlying mechanisms are unique and still worth studying.

1. Human Papillomavirus (HPV) and Cardiovascular Disease:

The studies in consideration establish a robust association between HPV infection and increased cardiovascular risk, particularly for atherosclerotic cardiovascular disease (ASCVD) and coronary artery disease (CAD). As an example, Kim et al. (2024) established a significant correlation between high-risk HPV (HR-HPV) infection and increased ASCVD and ischemic heart disease (IHD) mortality (9). Zhang et al. (2024) provided further evidence, with a meta-analysis finding that individuals with HPV are 40% more likely to develop cardiovascular disease and twice more likely to develop CAD than their HPV-negative counterparts (10). HPV infection likely promotes chronic inflammation, a known risk factor for atherosclerosis and cardiovascular disease. Liu et al.'s (2025) work found that cardiovascular health scores, such as Life's Essential 8 (LE8), are inversely related to HPV infection, in support of the hypothesis that improved cardiovascular health would reduce the risk of HPV (34).

Importantly, research carried out in 2025 by Yang et al., also puts forward the potential protection offered with the administration of vaccines against HPV (11). Through studies, they found that vaccine coverage correlated with reduced cardiovascular disease incidence rates, and that consequently points to vaccine administration in preventing cervical cancer but potentially offering broader cardiovascular protection. There should, however, be further research done to explore these measures of protection further.

2. Human Immunodeficiency Virus (HIV) and Cardiovascular Disease:

The connection between CVD and HIV infection exists. Research frequently shows that individuals with HIV are significantly more likely to suffer from arteriosclerosis, myocardial infarction, and stroke. This can be explained through chronic inflammation within the framework of HIV infection and side effects of antiretroviral therapy (ART) for the lipid profile. To clarify, Rodriguez et al. (2020) proved that long-term use of ART was related to the risk of myocardial infarction,(14) and Kebrit et al. (2020) proved that a 30% increased risk of cardiovascular disease was found in infected individuals with HIV in comparison to individuals without HIV infection (19). Some research indicated ART-inducted dysregulation of the lipid profile that fosters cardiovascular diseases due to the increase in cholesterol and triglycerides and that makes cardiovascular risk in this population more complicated.

Moreover, the stiffness of the carotid artery increases with HIV infection, indicated by Yang et al. (2022) (15)**.** Blood pressure is also elevated and arterial plaque accumulation stimulated through HIV (Mzoh et al., 2020), (20) and long-established HIV can create extensive arterial destruction and produce more cardiovascular events (Psichogious et al., 2019). These findings of the studies emphasize the crucial need for repeated cardiovascular monitoring in patients with HIV infection, particularly patients under long-term ART (23).

3. Epstein-Barr Virus (EBV) and Cardiovascular Disease:

The relationship between EBV infection and cardiovascular disease remains unclear and with inconsistent findings in research studies. There were certain studies that established a small but significant relationship but others failed to establish a significant relationship. For instance, Parikh et al. (2020) (29) established that EBV infection correlated with stroke risk in autoimmune disease patients but Panter et al. (2020) failed to establish EBV and coronary artery disease to be directly related but established that EBV-infected individuals had higher levels of C-reactive protein (CRP), which is an inflammatory marker (30). This means that EBV perhaps does not directly cause cardiovascular disease but contributes to the progression of vascular inflammation, especially in the presence of pre-existing disease states.

Studies like Sachinidis et al. (2022) and Chen et al. (2023) show that EBV infection would thus have the indirect effect towards cardiovascular risk, through worsening of pre-existing risk factor conditions like rheumatoid arthritis or autoimmune diseases. Larger studies will be required to confirm these findings and establish whether EBV plays more than a minor role in cardiovascular endpoints in a more direct way (31) (6).

5. CONCLUSION

The investigations examined in this review suggest that certain oncogenic viruses, such as HPV, HIV, and EBV, are possible causative agents in cardiovascular diseases owing to their contributions to chronic inflammation, immune system dysfunction, and antiviral therapy side effects. Those of HPV and HIV are more strongly associated with increased cardiovascular risk, but that of EBV is uncertain and warrants more studies. These findings would mean that infected individuals should be more closely observed and their cardiovascular risk evaluated. Large-scale and high-grade studies are necessitated to establish more certain causality and more effective prevention strategies in these individuals.

Limitations

1. Some studies included smaller sample sizes, which may limit the generalizability of the findings.
2. The variability in study designs and populations could affect the consistency of results.
3. Certain studies exhibited a potential risk of bias, particularly in data collection and reporting.
4. Not all studies accounted for potential confounding factors, which might impact the accuracy of the associations.
5. Several studies lacked long-term follow-up to assess the sustained impact of viral infections on cardiovascular outcomes.

Recommendations

1. Larger, multi-center studies are needed to validate and strengthen the current findings.
2. Standardized diagnostic criteria for both viral infections and cardiovascular diseases should be used across studies.
3. Longitudinal studies with extended follow-up periods are crucial to assess the long-term effects of cancer-causing viruses on cardiovascular health.
4. Further research should explore potential interventions that may mitigate the cardiovascular risks associated with viral infections.

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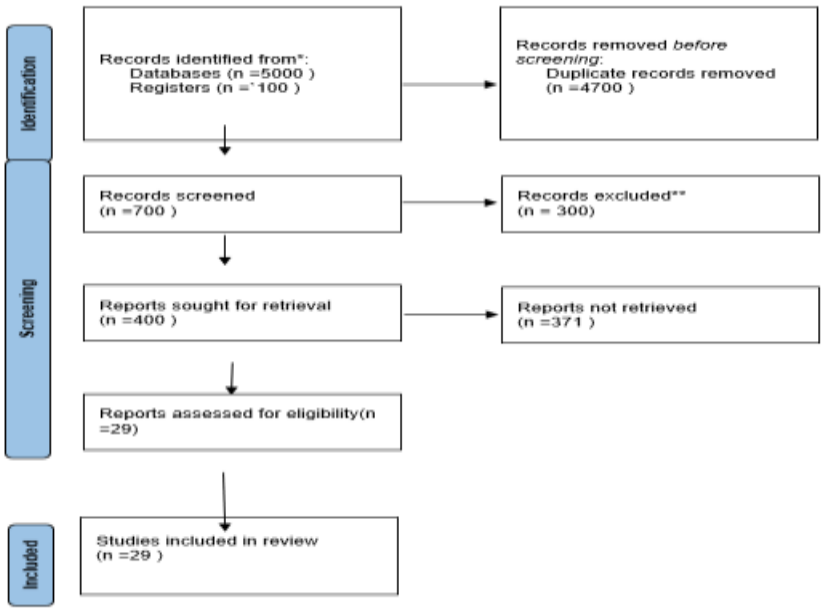
Conflict of Interest

The authors declare no conflict of interest.

PRISMA Flow Diagram



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