Epidemiology of Coronary Heart Disease in Patients With Human Immunodeficiency Virus

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As a growing number of patients infected with human immunodeficiency virus (HIV) have access to antiretroviral therapy and achieve virologic suppression, the focus of clinical care is shifting from treating the infectious complications of advanced immunodeficiency to managing and preventing chronic disease. The aging of the HIV-positive population and increased rates of chronic disease complications in the setting of HIV infection have increased the impact of noncommunicable diseases such as coronary heart disease (CHD). The effect of HIV on CHD is independent of traditional cardiovascular risk factors and antiretroviral medications and is likely due in part to the chronic inflammation and immune activation underlying HIV infection. This article describes the current state of epidemiologic knowledge on CHD in HIV infection. It highlights key studies in the field and summarizes epidemiologic data with respect to traditional and novel CHD risk factors, specialized clinical subgroups, and broader cardiovascular outcomes.

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KEY WORDS

Human immunodeficiency virus • Coronary heart disease • Antiretroviral therapy • Risk factors • Cardiovascular disease • Inflammation

As a growing number of patients infected with human immunodeficiency virus (HIV) have access to antiretroviral therapy (ART) and achieve virologic suppression, the focus of clinical care is shifting from treating the infectious complications of advanced immunodeficiency to managing and preventing chronic disease. The increased impact of noncommunicable diseases is due to both the aging of the HIV-positive population as a whole and to increased rates of chronic disease complications in the setting of HIV infection. Of these noninfectious complications, coronary heart disease (CHD) is of considerable import. In 2010, ischemic heart disease was the number one

cause of disability-adjusted life years globally and the number one cause of death, years of life lost, and disability-adjusted life years in the United States.[1] Extensive data over the past decade indicate that HIV infection confers an increased risk of CHD, with greater-than-expected morbidity and mortality from a disease that is already widespread.[2] Moreover, risk factors for HIV-associated CHD are thought to differ from those of the general population, with risk mediated by HIV-specific factors, including chronic inflammation and immune activation. Therapeutic interventions tailored to traditional CHD risk factors and proven to benefit the general population may therefore not be appropriate in the setting of HIV infection.

In recent years, our understanding of the epidemiology of CHD in HIV has evolved, reflecting clinical progress both in HIV medicine and in preventative cardiology. Recent studies feature improved characterization of demographic and clinical risk factors that modulate risk for HIV populations. This article describes the current state of epidemiologic knowledge on CHD in HIV infection. It highlights key studies in the field and summarizes epidemiologic data with respect to (1) traditional and novel CHD risk factors, (2) specialized clinical subgroups, and (3) broader cardiovascular outcomes. The review does not focus on mechanistic data or on clinical management, because other recent reviews and articles in this supplement summarize these topics.[3] Understanding the epidemiology of HIV-associated CHD has implications for the long-term care of both HIV-infected patients and of other at-risk populations with novel CHD risk factors.

CHD Risk in HIV Infection

HIV confers an increased risk of CHD across diverse geographic and clinical settings. Large epidemiologic studies spanning the past decade have investigated CHD and myocardial infarction (MI) rates in HIV cohorts compared with appropriate control participants and demonstrated consistently increased rates in the HIV groups, with magnitude of risk approximately doubled in the setting of HIV (Table 1).

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Following early case reports of cardiovascular disease (CVD) in HIV-infected patients and data on protease inhibitor (PI)-induced dyslipidemia,[4] several population-based studies investigated associations among HIV, ART, and CHD in the early 2000s. In an ongoing study of electronic health record (EHR) data from Kaiser Permanente in Northern California that was recently updated, Klein and colleagues[5] were among the first to demonstrate significantly higher CHD (6.5 vs 3.8; $P = .003$) and MI (4.3 vs 2.9; $P = .07$) hospitalization rates comparing HIV-infected men with control patients in the closed health care system. These data were corroborated by Currier and associates,[6] who showed CHD incidence to be significantly increased in an HIV-infected group versus a population-based control group in a study of California Medicaid administrative claims data from more than 3 million individuals. The finding of increased risk in HIV was present for both men (relative risk [RR] 6.76; 95% confidence interval [CI], 3.36-13.58 for those aged 18-24 y; and RR 2.16; 95% CI, 1.81-2.58 for those aged 25-34 y) and women (RR 2.47; 95% CI, 1.23-4.95 for those aged 18-34 y; RR 1.53; 95% CI, 1.10-2.13 for those aged 35-34 y; and RR 1.67; 95% CI, 1.41-1.97 for those aged 35-44 y), although it did not persist above age 34 for men or above age 44 for women. This was the first major study to demonstrate a stronger association of HIV with cardiovascular outcomes in younger age groups, in which the absolute risk of events is lower but the RR comparing HIV with non-HIV disease is higher. Further data from the French Hospital Database on HIV (FHDH) showed validated MI incidence rates to be increased in a large cohort of HIV-infected men exposed to PI therapy for at least 18 months, comparing rates with those calculated for the French general male population (age-adjusted standardized morbidity ratio 0.8, 95% CI, 0.5-1.3 for PI exposure < 18 mo; 1.5, 95% CI, 0.8-2.5 for PI exposure 18-29 mo; 2.9, 95% CI, 1.5-5.0 for PI exposure > 30 mo).[7]

Further studies reinforced these early findings, accounting for additional possible confounding factors. A study from the Partners HealthCare System in Boston showed MI incidence rates to be increased in HIV-infected patients versus more than 1 million patients comprising the health care system–based control group. The RR for MI was 1.75 (95% CI, 1.51-2.02) in a model adjusted for demographics and common CHD risk factors.[8] A Danish study compared rates of first hospitalization for ischemic heart disease in HIV-infected patients versus a population-based control group and found patients with HIV to be at significantly increased risk (adjusted RR 2.12;

TABLE 1

Summary of Epidemiologic Studies of HIV and CHD

Study	N (HIV)[a]	Control Group	Women (%)	Age HIV[b]	Time Period	HIV Follow-up (y)	Primary Result	Effect Size
Klein D et al[5]	4159	Random sample Kaiser Permanente members	0	Mean 44	1996-2001	4.1	↑ MI and CHD in HIV vs control subjects	1.5 (MI) 1.7 (CHD)
Currier JS et al[6]	28,513	Patients enrolled in CA Medicaid > 1 y	27	46% men and 35% women aged 35-44	1994-2000	2.5	↑ CHD in HIV (age 18-33) vs control subjects	2.06
Mary-Krause M et al[7]	34,976	Estimated rates from French male general population	0	Mean 38	1996-1999	2.8	↑ MI in HIV with PI exposure > 18 mo vs general population	1.5 (PI 18-29 mo) 2.9 (PI ≥ 30 mo)
Triant VA et al[8]	3851	Controls from health care system-based data registry	30	Median 38	1996-2004	4.5	↑ incident MI in HIV vs control subjects	1.75
Obel N et al[9]	3953	Population-based control group matched 95:1 on sex, age, residence	23	Median 37	1995-2004	5.2	↑ first hospitalization for CHD in HIV on ART vs control subjects	2.12
Lang S et al[10]	74,958	Three population-based French registries	11	Median 47	2000-2006	—	↑ MI in HIV vs 3 population registries	1.5
Durand M et al[11]	7053	Control group on sex, age, entry date, duration insurance	22	Median 37	1985-2007	4.2	↑ MI in HIV vs 4:1 matched control subjects	2.11
Freiberg MS et al[13]	27,350	Controls from VACS matched on age, race, site, calendar year	3	Median 49	2003-2009	5.9	↑ MI in HIV vs 2:1 matched control	1.48
Silverberg M et al[14]	22,081	HIV-uninfected Kaiser members	9	40% aged 35-44	1996-2009	4.5	↑ MI in HIV vs controls	1.4

[a]Number of HIV patients in study; [b]age of HIV patients at baseline. ART, antiretroviral therapy; CA, California; CHD, coronary heart disease; HIV, human immunodeficiency syndrome; MI, myocardial infarction; PI, protease inhibitor; VACS, Veterans Aging Cohort Study.

95% CI, 1.62-2.76).[9] In updated data from the FHDH cohort, MI incidence was increased for the HIV group compared with sex- and age-standardized rates from the general French population, with a standardized morbidity ratio of 1.5 (95% CI, 1.3-1.7).[10] Similar results were demonstrated in a Quebec HIV cohort in which MI incidence was elevated for the HIV group compared with a matched control group, with an adjusted incidence ratio of 2.11 (95% CI, 1.69-2.63).[11] Taken together, these earlier data from multiple discrete cohorts suggested the presence of increased CHD risk in the setting of HIV that is independent of demographics or traditional CHD risk factors.

Recent studies linking HIV infection to CHD have further expanded on prior investigations, refining strategies to confirm outcome measures and accounting for additional possible confounding factors. Moreover, recent data reflect contemporary trends in cardiovascular medicine, with decreasing MI rates in the general population, and

in HIV medicine, with utilization of new and less metabolically toxic antiretroviral medications. In a recent meta-analysis, HIV-infected patients were shown to have a 61% increased RR of CVD endpoints.[12] Compared with non–HIV-infected patients, the RR of CVD was increased among HIV-infected patients not on ART (RR 1.61; 95% CI, 1.43-1.81), as well as those on ART (RR 2.00; 95% CI, 1.70-2.37). There was a 50% increase in risk comparing HIV-infected patients on ART with those not on ART. Limitations of the analysis reflect those of observational research in general and include unmeasured confounding and inadequate or nonhomogenous HIV-uninfected control groups.

In a recent investigation from the Veterans Aging Cohort Study virtual cohort,[13] more than 27,000 HIV-infected patients (primarily men) were compared with respect to MI rates with HIV-uninfected patients with similar demographics and behavior patterns. Rates of MI were significantly increased for the 40 to 49 (incidence rate ratio [IRR] 1.34; 95% CI, 1.04-1.72), 50 to 59 (IRR 1.80; 95% CI, 1.47-1.21), and 60 to 69 (IRR 1.53; 95% CI, 1.03-2.26) age groups. The hazard ratio (HR) for MI associated with HIV status was 1.48 (95% CI, 1.27-1.72), in modeling adjusted for traditional CHD risk factors, comorbid medical conditions, and substance use. Notably, the association remained significant in patients with undetectable HIV ribonucleic acid (RNA) (HR 1.39; 95% CI, 1.17-1.66). Adjudicated outcomes, the ability to capture out-of-system events, and ascertainment of many possible confounding factors contribute to the strength of the analysis. Most recently, Silverberg and colleagues[14] published a study updating their original MI data, assessing MI risk in HIV from 1996 to 2009 in more than 250,000 patients, including more than 22,000 HIV-infected patients and demographically matched controls. Although HIV infection was significantly associated with MI in an analysis of all patients (RR 1.4; 95% CI, 1.3-1.6), there was no significant difference in MI rates comparing HIV-infected patients with recent or nadir CD4 count $\geq$ 500 and HIV-negative patients. Strengths of this analysis include long follow-up time, ability to adjust for sociodemographic factors, including census-based socioeconomic status, and a closed health delivery system with increased likelihood of capturing complete risk factor and outcome data.

What factors drive the observed increase in CHD risk, and which HIV-infected patients confront the highest risk? What are the implications for the clinical management of CHD in HIV-positive populations? Although the summarized studies considered the RR of CHD in HIV infection, further epidemiologic data have informed us about (1) traditional and novel CHD risk factors in HIV, (2) clinical and sociodemographic HIV subgroups at heightened risk, and (3) broader cardiovascular outcomes. These data are highlighted next.

Role of CHD Risk Factors

Established CHD Risk Factors

An extensive body of literature has established increased rates of traditional CHD risk factors in HIV-infected patients compared with non–HIV-infected control groups. Dyslipidemia, diabetes, and hypertension have been shown to be more prevalent, with lipid profiles typically characterized by hypertriglyceridemia and low high-density lipoprotein cholesterol.[4] Smoking is also extremely prevalent and poses a significant challenge to HIV-infected patients and their providers.[15] Although modifying traditional CHD risk factors is an important component of preventative care for HIV-infected populations, these factors have not been shown to account for the entirety of observed increased CHD risk, suggesting that novel factors play a role in mediating risk. Risk factors attributable directly or indirectly to HIV infection are likely to participate in the complex interplay of CHD risk and are summarized in Table 2.

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HIV-related CHD Risk Factors

ART. Evidence of PI-associated dyslipidemia[4] initially prompted consideration of ART as a contributor to HIV-associated CHD, a complex issue due to the heterogeneity and concomitant use of HIV medications. Early studies on the association of ART and MI conflicted with regard to findings.[5-7,16] A large observational study from the Data Collection on Adverse Events of Anti-HIV Drugs Study Group, designed to investigate the effects of ART exposure on MI risk, showed an increased RR of MI attributable largely to the PI class of medications and independent of lipids (adjusted RR of MI 1.16 per year of ART exposure).[17] Studies of specific medications implicated several of the older PIs not widely used today,[18,19] although newer PIs have not been shown to be associated with increased risk.[20] Recently,

TABLE 2

Risk Factors Associated With HIV Disease

Traditional	Novel	High Relative Risk HIV Subgroups
Smoking	Inflammation HIV viremia	Young age groups
Dyslipidemia	Immune dysfunction Low CD4 count	Women
Diabetes Glucose intolerance Insulin resistance Hypertension Visceral adiposity	Antiretroviral medications Selected protease inhibitors Abacavir	HCV coinfected

HCV, hepatitis C virus; HIV, human immunodeficiency virus.

two meta-analyses based on observational data concluded MI risk to be increased with the PI class of drugs.[12,21] The effects of nucleoside reverse transcriptase inhibitors—particularly abacavir—on CHD risk has prompted extensive investigation.

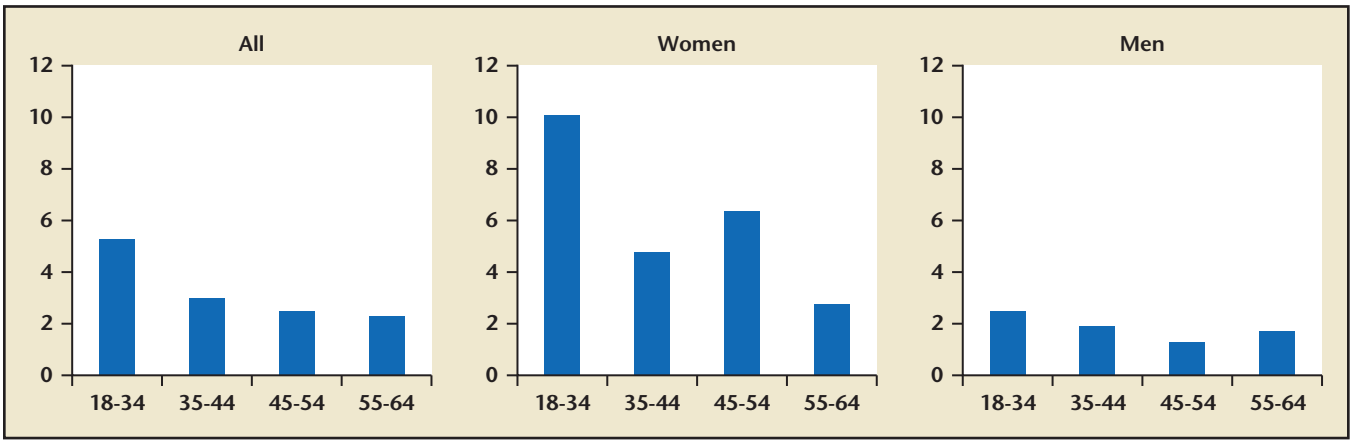
HIV Disease Parameters. Further adding to the complexity of the interplay of risk factors for CHD in HIV populations is HIV disease stage. Clinically measured HIV disease parameters, including CD4 count, which represents the degree of immune reconstitution, and HIV RNA or viral load, which indicates the level of viremia, have been correlated with CHD risk. Low recent[22,23] and nadir[14] CD4 counts have been associated with CVD outcomes in several studies. Cardiovascular outcomes have also been shown to relate to increased or detectable HIV RNA across several studies.[13,24,25] These data support the hypothesis that MI risk is mediated, at least in part, by degree of control of HIV. Patients who have uncontrolled viremia, are more immunosuppressed, or reached a more profound degree of immunosuppression prior to ART initiation appear to be at heightened CHD risk. These data suggest that initiation of ART earlier in the course of disease would be beneficial from a CHD standpoint, a hypothesis that will be tested through the ongoing Strategic Timing of Antiretroviral Treatment trial.

CHD Risk in HIV Subgroups

Women

HIV may uniquely impact women with respect to CHD risk. Women differ from men on the basis of both CHD risk factors and HIV-related factors, yet are historically underrepresented in both HIV clinic trials and observational studies (Table 1). Available observational data suggest a striking difference in RR of CHD for HIV-infected women, with HIV conferring a risk increase (relative to non-HIV counterparts) of double for women compared with men in several studies (Figure 1).[8,10] For example, the RR of MI conferred by HIV status was 2.98 for women versus 1.4 for men in the Partners HIV cohort.[8] Results from the FHDH cohort were strikingly similar, with sex- and age-standardized morbidity ratios of 2.7 for women and 1.4 for men.[10] This increased RR has been shown to translate into increased mortality attributable to CVD.[26] The sex-specific determinants

Figure 1. Incidence rate ratios comparing relative rates of myocardial infarction in HIV-infected versus control patients according to age group and sex. HIV, human immunodeficiency virus. Data from Triant VA et al.[8]



of HIV-associated CHD are an important priority for future study.

Resource-limited Settings

The effect of HIV on CHD in resource-limited settings is a significant yet understudied area. As a vast number of patients will be living with treated HIV infection in a region with escalating levels of CVD, the dual impact of these epidemics is likely to be substantial. Although data suggest that CHD risk factors are indeed prevalent in HIV-positive populations in resource-limited settings,[27] data on cardiovascular outcomes are scarce,[28] with no studies to date comparing MI rates in HIV-positive patients versus matched control patients. A complete discussion of this important topic is beyond the scope of this review. An enhanced understanding of this area will have important implications for developing strategies for CHD risk-factor modification in HIV groups and for considering ways to integrate HIV and noncommunicable disease health care delivery systems globally.

Hepatitis C Virus Coinfection

Patients coinfected with the hepatitis C virus (HCV) represent an important clinical subgroup that may differ in terms of risk factor distribution and inflammatory profile compared with patients infected with HIV alone. HCV itself may increase CHD risk, and the effect of coinfection on cardiovascular risk has begun to be delineated. Although two studies have demonstrated increased risk of cardiovascular outcomes in coinfected patients compared with HIV monoinfected patients,[29,30] another study did not find a significant difference between the two groups.[31] A finding of heightened risk in this subgroup would enable CHD preventive efforts to be further tailored to HIV-infected patients with clinical comorbidities that place them at the highest risk.

Cardiovascular Outcomes

HIV appears to exert a wide range of effects on the heart and vasculature. In the early era of ART, HIV-infected patients were found to have increased rates of cardiomyopathy, a finding that was thought to be related to direct viral effects. As the data on CHD have continued to accumulate, broader cardiovascular endpoints have been examined and have been shown to be similarly modulated by HIV and its presumed accompanying inflammatory and immunologic effects. Specifically, HIV infection has been linked with ischemic stroke,[25,32] peripheral arterial disease,[33] congestive heart failure,[34] and sudden cardiac death.[35]

Implications of Epidemiologic Data

Taken together, epidemiologic studies investigating the risk of CHD in HIV-positive populations suggest that being infected with HIV confers increased risk, with an effect 1.5- to 2-fold higher than baseline risk, comparable with that observed in other inflammatory disorders. This effect persists in the current era characterized by decreasing incidence of atherosclerotic CVD in the general population. Interestingly, the impact of HIV on CHD has been shown to be most pronounced in demographic groups typically considered low risk. Although the absolute risk of MI within HIV-positive populations is higher among men, the relative increase in risk comparing HIV-infected to non–HIV-infected populations is higher among women, with several studies showing double the RR for HIV-infected women versus HIV-infected men.[8,10] A similar effect is true for age. The highest absolute risk of MI among HIV-infected patients occurs in the oldest age groups, yet the RR, comparing each age stratum with appropriately matched control patients, is highest in the youngest age groups and decreases with increasing age.[6,8] These data suggest that our typical conception of a "low-risk patient" is likely not to be applicable in the setting of HIV, thereby necessitating increased vigilance on the part of HIV-infected patients and providers with respect to cardiovascular risk.

Coupled with rapidly accumulating mechanistic data, epidemiologic data suggest that CHD risk is modulated by HIV disease characteristics. The link between CHD risk and higher levels of viremia and more profound immunosuppression observed in epidemiologic studies reinforces the hypothesis that the degree of underlying inflammation and immune activation affect an individual's cardiovascular risk. These data suggest that earlier treatment of HIV, endorsed by the most recent HIV treatment guidelines,[36] could decrease cardiovascular risk. Yet several recent studies indicate that increased cardiovascular risk persists even in the setting of controlled HIV disease as evidenced by undetectable HIV RNA,[12,13] postulated to be due to ongoing low levels of viral replication and associated inflammation. This finding

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suggests that cardiovascular risk will continue to be an important consideration for an aging HIV population, even with health optimized from an HIV and from a cardiovascular risk factor perspective. Tailored cardiovascular interventions are needed, beyond traditional risk factor modification and virologic suppression with ART, to eliminate this residual risk for a vast group of at-risk patients.

Observational research provides invaluable data by investigating large patient groups and long-term outcomes that cannot be studied in clinical trials; yet such studies must always be considered in the context of limitations intrinsic to observational cohort research. As with clinical trials, observational studies are not necessarily broadly representative, depending on the study population. For example, the two most recent studies of CHD risk in HIV populations were largely limited to men (97% and 91%, respectively),[13,14] making generalizability to HIV-infected women, who may differ with regard to CHD and HIV risk factors, problematic. All studies are subject to the possibility of unmeasured confounding, although recent studies have used rigorous approaches to account for a broad range of sociodemographic and clinical factors that might affect risk.[13,14] Finally, the problem of capturing out-of-system outcome events can impact study results; recent studies utilizing multiple data sources or being conducted in closed systems have attempted to minimize this limitation.[13,14] Methods to optimize use of EHR data, including selection of appropriate populations and control groups, improved characterization of risk factor data, and enhanced methods to control for confounding will be extremely important clinical research tools as EHR sources of data are increasingly widespread.

Conclusions

The intersection of CHD and HIV represents a significant clinical challenge from both the cardiovascular and HIV medicine standpoints. HIV appears to nearly double cardiovascular risk, yet a high-risk HIV patient differs from what we might expect clinically and demographically. The effect of HIV on CHD persists over time, is independent of traditional cardiovascular risk factors and antiretroviral medications, and is likely due in large part to the chronic inflammation and immune activation underlying HIV infection. Salient gaps in our current knowledge include the relative determinants of CHD in HIV populations, the specific effects of HIV on CHD outcomes in women, and the association between HIV and cardiovascular disease in resource-limited settings. A fundamental question that remains to be definitely answered is whether HIV should be considered a cardiovascular risk factor that increases an individual's risk, meriting aggressive intervention, as in the case of diabetes. Available epidemiologic data suggesting this to be the case have spurred ongoing mechanistic studies and clinical trials to solidify our understanding. Findings from these studies will enable the development of tailored and evidence-based clinical strategies to reduce CHD in the HIV-infected population. Moreover, HIV-infected patients could serve as a prototype of a patient population with CHD risk based on nontraditional factors, whose optimal management is not necessarily being captured by the most recent general population guidelines and paradigms on cardiovascular risk reduction. Continued expansion of knowledge of this important convergence of diseases will have important implications for both HIV and cardiovascular medicine. ■

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MAIN POINTS

- Extensive data indicate that human immunodeficiency virus (HIV) infection confers an increased risk of coronary heart disease (CHD), with greater-than-expected morbidity and mortality.
- Risk factors for HIV-associated CHD are thought to differ from those of the general population; traditional CHD risk factors have not been shown to account for the entirety of observed increased risk, suggesting that novel HIV-related factors such as inflammation and immune activation play a role in mediating risk.
- Modifying traditional CHD risk factors is an important component of preventative care for HIV-infected populations.
- Interventions targeting HIV-specific risk factors may further decrease CHD risk for this population.
- A fundamental question that remains to be definitely answered is whether HIV should be considered a cardiovascular risk factor that increases an individual's risk.