## Inflammatory Markers and the Risk of Coronary Heart Disease in Men and Women

Jennifer K. Pai, M.H.S., Tobias Pischon, M.D., M.P.H., Jing Ma, M.D., Ph.D., JoAnn E. Manson, M.D., Dr.P.H., Susan E. Hankinson, Sc.D., Kaumudi Joshipura, B.D.S., Sc.D., Gary C. Curhan, M.D., Sc.D., Nader Rifai, Ph.D., Carolyn C. Cannuscio, Sc.D., Meir J. Stampfer, M.D., Dr.P.H., and Eric B. Rimm, Sc.D.

## **ABSTRACT**

Background Few studies have simultaneously investigated the role of soluble tumor necrosis factor (TNF-a) receptors types 1 and 2 (sTNF-R1 and sTNF-R2), C-reactive protein, and interleukin-6 as predictors of cardiovascular events. The value of these inflammatory markers as independent predictors remains controversial.

Methods We examined plasma levels of sTNF-R1, sTNF-R2, interleukin-6, and C-reactive protein as markers of risk for coronary heart disease among women participating in the Nurses' Health Study and men participating in the Health Professionals Follow-up Study in nested case—control analyses. Among participants who provided a blood sample and who were free of cardiovascular disease at baseline, 239 women and 265 men had a nonfatal myocardial infarction or fatal coronary heart disease during eight years and six years of follow-up, respectively. Using risk-set sampling, we selected controls in a 2:1 ratio with matching for age, smoking status, and date of blood sampling.

Results After adjustment for matching factors, high levels of interleukin-6 and C-reactive protein were significantly related to an increased risk of coronary heart disease in both sexes, whereas high levels of soluble TNF-or receptors were significant only among women. Further adjustment for lipid and nonlipid factors attenuated all associations; only C-reactive protein levels remained significant. The relative risk among all participants was 1.79 for those with C-reactive protein levels of at least 3.0 mg per liter, as compared with those with levels of less than 1.0 mg per liter (95 percent confidence interval, 1.27 to 2.51; P for trend <0.001). Additional adjustment for the presence or absence of diabetes and hypertension moderately attenuated the relative risk to 1.68 (95 percent confidence interval, 1.18 to 2.38; P for trend = 0.008).

Conclusions Elevated levels of inflammatory markers, particularly C-reactive protein, indicate an increased risk of coronary heart disease. Although plasma lipid levels were more strongly associated with an increased risk than were

inflammatory markers, the level of C-reactive protein remained a significant contributor to the prediction of coronary heart disease.

## **Source Information**

From the Departments of Epidemiology (J.K.P., T.P., J.E.M., S.E.H., K.J., G.C.C., M.J.S., E.B.R.) and Nutrition (T.P., M.J.S., E.B.R.), Harvard School of Public Health; the Division of Preventive Medicine (J.K.P., J.E.M.) and Channing Laboratory (T.P., J.M., S.E.H., G.C.C., M.J.S., E.B.R.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; the Department of Oral Health Policy and Epidemiology, Harvard School of Dental Medicine (K.J.); the Department of Laboratory Medicine, Children's Hospital (N.R.); and the Department of Pathology, Harvard Medical School (N.R.) — all in Boston; the Department of Epidemiology, German Institute of Human Nutrition, Potsdam-Rehbruecke, Germany (T.P.); and Merck Research Laboratories, West Point, Pa. (C.C.C.).