Dietary Iron Intake and Risk of Coronary Disease Among Men

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Background We prospectively studied iron intake in relation to the incidence of coronary disease in a 4-year follow-up of 44 933 men (with no previous history of cardiovascular disease) aged 40 to 75 years in 1986 who completed a food frequency questionnaire at baseline.

Methods and Results We documented 844 incident cases of coronary disease (249 nonfatal myocardial infarctions, 137 coronary disease fatalities, and 458 bypass operations or angioplasties). After adjustment for established risk factors, there was no significant association between total iron intake and risk of coronary heart disease. Men in the highest quintile of total iron intake (median, 37 mg/d) had a relative risk (RR) of fatal coronary disease or nonfatal myocardial infarction of 0.73 (95% confidence intervals [CI], 0.51, 1.06) compared with men in the lowest quintile of intake (median, 11 mg/d). Dietary intake of heme iron—mainly from red meat—also was not significantly associated with risk of coronary heart disease. However, incidence of fatal coronary disease or nonfatal myocardial infarction was higher among men in the top quintile of heme iron intake compared with men in the lowest quintile (RR, 1.42; 95% CI, 1.02, 1.98). This association remained after adjustment for dietary cholesterol and fats. Heme iron but not total iron intake was positively correlated with serum ferritin among 123 members of the cohort who participated in a validation study.

Conclusions These results do not support the hypothesis that dietary iron in general increases coronary risk in men; they are consistent, however, with an increased risk of myocardial infarction among men with higher intake of heme iron, which is itself positively associated with iron stores. (***Circulation*. 1994;89:969-974.**)

Key Words • heart disease • diet • risk factors

Free iron—a catalyst of the production of free radicals—has been implicated in lipid peroxidation[1] and ischemic myocardial damage.[2,3] However, direct evidence that high stored iron levels or high iron intake affects the incidence of coronary disease in humans is limited. In a recent Finnish prospective study, serum ferritin and dietary intake of iron were strongly associated with risk of myocardial infarction.[4] In a larger study conducted in the United States, no significant association was found between serum ferritin and risk of myocardial infarction.[5] We report here the association between iron intake and the risk of coronary disease in a large prospective study among US men. Because the absorption of heme iron is more complete and less well regulated than that of nonheme iron,[6] we also examined the specific association of heme iron intake with coronary disease incidence.

Methods

Health Professionals Follow-up Study

The Health Professionals Follow-up Study is a prospective investigation of dietary etiologies of heart disease and cancer among 51 529 health professionals aged 40 to 75 years.[7] The study began in 1986 when cohort members completed a detailed food frequency questionnaire and provided information about medical history, heart disease risk factors, and dietary changes during the past 10 years. Follow-up questionnaires were sent in 1988 and 1990. We excluded from analysis 1530 men who did not satisfy the a priori criteria of daily caloric intake between 800 and 4200 kcal and fewer than 70 blanks out of 131 total listed food items. In addition, we excluded men who reported on the 1986 questionnaire a diagnosis of myocardial infarction, angina, coronary artery surgery, stroke, transient ischemic attack, or peripheral arterial disease. One or more of the above conditions were met by 5066 participants, leaving 44 933 eligible men who were followed for coronary disease incidence in the subsequent 4 years. We confirmed disease status of over 96% of eligible participants from each 2-year follow-up cycle.

Dietary Assessment

The semiquantitative food frequency questionnaire completed in 1986 included questions regarding average frequency of intake of 131 foods over the previous year. Ten additional questions were asked specifically about current vitamin and mineral supplement use, including type and categories of dose and duration. We also asked participants to identify specific brands of multiple vitamins, cooking oils, and cereals.[7,8] The validity of the food frequency questionnaire was assessed in a random sample of 127 men living in the Boston area. Nutrient intake from the food frequency questionnaire was compared with two 1-week diet records spaced approximately 6 months apart.[9] Pearson correlation coefficients between the diet records and the dietary questionnaire were adjusted for total energy intake[10] and for within-person variability in daily intake.[11] The correlation coefficient for total iron intake was .50. Plasma ferritin concentrations were determined in a sample of 123 men. Plasma ferritin was positively correlated with intake of heme iron (Spearman correlation coefficient: $r=.16$, $P=.07$) and of beef, pork, and lamb ($r=.22$, $P=.03$) but not with intake of total iron ($r=-.15$, $P=.08$).

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Case Ascertainment

Methods of case ascertainment have been described previously in detail.[8] Briefly, fatal coronary disease (including sudden death), nonfatal myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty occurring between the return of the baseline questionnaire and January 31, 1990, were considered as end points. Participants who reported an incident myocardial infarction on the 1988 or 1990 questionnaire were sent a letter to confirm the report and to request permission to review medical records. A nonfatal myocardial infarction was confirmed using World Health Organization criteria[12]: compatible symptoms plus either typical ECG changes or elevation of cardiac enzymes. Deaths were reported by next-of-kin, coworkers, postal authorities, or the National Death Index. Fatal coronary diseases were confirmed using medical records or autopsy reports. Fatal coronary disease was also considered confirmed if it was the underlying cause on the death certificate and a diagnosis of incident coronary disease was confirmed by records or interviews with family members. The cause listed on the death certificate alone was not accepted as confirmation of fatal coronary disease. Sudden death, defined as death within 1 hour of the onset of symptoms in individuals with no previous serious illness or other plausible cause of death (other than coronary disease), was included as fatal coronary disease. For subjects with multiple end points, only the first was included in the analysis. Physicians reviewing medical records were blinded to the report of dietary intake.

Statistical Analysis

Each participant contributed follow-up time from the date of return of the 1986 questionnaire until a diagnosis of an end point, death, or January 31, 1990 (the date the 1990 questionnaire was initially mailed). Relative risks were calculated as the incidence rate of coronary disease among men in each category of iron intake divided by that rate among men in the lowest category of intake. We adjusted relative risks for age (5-year categories) using the Mantel-Haenszel method.[13] The Mantel extension test[14] was used to test for a linear trend. To adjust for other risk factors, we used multiple logistic regression to generate odds ratios as an estimate of relative risk. In multivariate logistic models, we tested for significant monotonic trends by assigning each participant the median value of the category and modeling this as a continuous variable. Differences in trends between subsamples of the study population were tested assuming a normal distribution of the corresponding regression coefficients. All probability values are two sided.

TABLE 1. Relation of Potential Risk Factors for Coronary Disease to Intake of Energy-Adjusted Iron and Heme Iron*

	Quintile of Energy-Adjusted Total Iron Intake				
	1	2	3	4	5
Energy-adjusted iron, mg/d (median)	11	13	15	18	37
Smokers, %	14.2	10.4	8.4	6.9	8.0
Alcohol, g/d	15.9	12.0	10.7	10.0	10.6
Body mass index, kg/m^2	25.0	25.1	25.1	24.8	24.6
Dietary fiber, g/d	16.2	20.4	23.4	26.6	24.4
Saturated fat, g/d (mean)	24.4	26.1	26.4	25.4	23.3
Cholesterol, g/d (mean)	282	334	357	346	313
Calories from fat, %	33.1	33.5	32.9	31.4	31.1
Vitamin E, IU/d	55.8	63.0	66.8	82.0	193.2
Vitamin C, mg/d	295	327	359	413	683
Carotene, IU/d (mean)	6182	9057	10 838	12 281	11 402
	Quintile of Energy-Adjusted Heme Iron Intake				
	1	2	3	4	5
Energy-adjusted heme iron, mg/d (median)	0.7	1.0	1.3	1.6	2.1
Smokers, %	6.4	8.4	10.0	10.7	12.6
Alcohol, g/d	11.1	12.4	12.7	12.2	10.7
Body mass index, kg/m^2	24.3	24.7	24.9	25.2	25.5
Dietary fiber, g/d	25.7	22.8	22.2	21.2	18.9
Saturated fat, g/d (mean)	21.7	23.5	25.9	27.0	27.5
Cholesterol, g/d (mean)	245	295	334	363	395
Calories from fat, %	28.8	30.9	32.4	33.9	36.1
Vitamin E, IU/d	113	94.8	89.7	78.9	82.5
Vitamin C, mg/d	493	426	412	377	360
Carotene, IU/d (mean)	11 650	10 258	9942	9640	8819

*Directly standardized to the age distribution of the entire cohort.

Results

During 157 010 person-years of follow-up, we documented 844 coronary events. This included 137 coronary heart disease deaths, 249 nonfatal myocardial infarctions, and 458 coronary bypass grafts or percutaneous transluminal coronary angioplasties.

The median intake of energy-adjusted total iron was 11 mg/d among men in the bottom quintile and 37 mg/d among men in the top quintile. Comparable numbers for intake of energy-adjusted heme iron were 0.7 mg/d and 2.1 mg/d (Table 1). Total iron intake was inversely associated with smoking, directly associated with intake of vitamins and fiber, and only slightly or not associated with dietary fats. In contrast, heme iron intake was directly associated with smoking, inversely associated with intake of fiber and vitamins, and directly associated with dietary fats (Table 1). Because of the small contribution of heme iron to total iron intake, differences in total iron intake between individuals are almost entirely accounted for by differences in intake of nonheme iron (correlation coefficient of total iron intake with nonheme iron intake, r=.99). Being almost identical to those for total iron intake, results for nonheme iron intake have not been included in this report.

When adjusted for age and energy intake, intake of total iron was associated with a decreased risk of myocardial infarction; the relative risk (RR) for the highest versus the lowest quintile was 0.72 (95% confidence intervals [CI], 0.51, 1.00; P for trend, .02). Intake of heme iron, similarly adjusted, was associated with an increased risk of myocardial infarction. The relative risk for the highest compared with the lowest quintile was 1.68 (95% CI, 1.23, 2.29). Neither total iron nor heme iron intake was associated with risk of coronary artery surgery. The association of heme iron intake with risk of fatal coronary disease (RR, 2.33; 95% CI, 1.36, 3.98) was stronger than its association with risk of nonfatal myocardial infarction (RR, 1.44; 95% CI, 0.98, 2.10) (Table 2).

TABLE 2. Age-Adjusted Relative Risk of Coronary Disease According to Intake of Energy-Adjusted Iron and Heme Iron

		Quintile						
		1	2	3	4	5	χ_1 Trend	*P*
Total iron								
CABG	RR	1.0	1.29	0.86	0.94	0.93	−1.30	.19
	(95% CI)	. . .	(0.98, 1.70)	(0.64, 1.17)	(0.70, 1.26)	(0.70, 1.25)		
Nonfatal myocardial infarction	RR	1.0	1.06	1.07	0.80	0.64	−2.53	.01
	(95% CI)	. . .	(0.72, 1.54)	(0.74, 1.55)	(0.54, 1.20)	(0.42, 0.97)		
Fatal CHD	RR	1.0	1.24	1.19	1.26	0.89	−0.39	.70
	(95% CI)	. . .	(0.72, 2.13)	(0.69, 2.04)	(0.74, 2.14)	(0.50, 1.56)		
Total myocardial infarction*	RR	1.0	1.11	1.10	0.94	0.72	−2.27	.02
	(95% CI)	. . .	(0.82, 1.52)	(0.81, 1.50)	(0.69, 1.30)	(0.51, 1.00)		
Heme iron								
CABG	RR	1.0	0.96	1.08	1.05	0.97	0.15	.85
	(95% CI)	. . .	(0.71, 1.28)	(0.81, 1.43)	(0.79, 1.40)	(0.72, 1.31)		
Nonfatal myocardial infarction	RR	1.0	1.11	0.86	1.27	1.42	1.91	.06
	(95% CI)	. . .	(0.74, 1.67)	(0.56, 1.33)	(0.86, 1.87)	(0.97, 2.08)		
Fatal CHD	RR	1.0	1.34	1.51	1.63	2.33	3.16	.001
	(95% CI)	. . .	(0.73, 2.43)	(0.84, 2.72)	(0.92, 2.90)	(1.36, 3.98)		
Total myocardial infarction*	RR	1.0	1.18	1.05	1.37	1.68	3.41	.0007
	(95% CI)	. . .	(0.84, 1.65)	(0.74, 1.49)	(1.00, 1.90)	(1.23, 2.29)		

CABG indicates coronary artery bypass graft; CHD, coronary heart disease; RR, relative risk; and CI, confidence intervals.
*Includes nonfatal myocardial infarction and fatal CHD.

After adjustment for established risk factors for coronary disease, both the inverse association of total iron and the direct association of heme iron intake with risk of myocardial infarction were attenuated. The relative risk of myocardial infarction for the highest compared with the lowest quintile of total iron intake was 0.73 (95% CI, 0.51, 1.06; *P* for trend, .03). The comparable figure for heme iron intake was 1.42 (95% CI, 1.02, 1.98; *P* for trend, .02) (Table 3). After further simultaneous adjustment for use of aspirin, physical activity, and intake of dietary fiber, carotene, and vitamin C, the relative risk for the highest compared with the lowest quintile of heme iron intake was 1.39 (95% CI, 0.99, 1.96; *P* for trend, .04).

Adjustment for dietary fats and particularly of cholesterol in the analyses is potentially important because of their correlation with intake of heme iron. After adjustment for saturated fat and dietary cholesterol, the relative risk of myocardial infarction for the highest versus the lowest quintile of heme iron intake was 1.48 (1.01, 2.16; *P* for trend, .03) (Table 3). Further adjustment for total dietary fat, polyunsaturated fat, and

TABLE 3. Multivariate* Relative Risk of Coronary Disease According to Intake of Energy-Adjusted Heme Iron

		Quintile					
		1	2	3	4	5	*P*, Trend
CABG	RR	1.0	0.92	1.01	0.95	0.82	.29
	(95% CI)	. . .	(0.68, 1.24)	(0.75, 1.35)	(0.71, 1.28)	(0.61, 1.12)	
Nonfatal myocardial infarction	RR	1.0	1.11	0.86	1.21	1.24	.20
	(95% CI)	. . .	(0.74, 1.67)	(0.56, 1.34)	(0.81, 1.82)	(0.83, 1.86)	
Fatal CHD	RR	1.0	1.28	1.36	1.39	1.84	.03
	(95% CI)	. . .	(0.70, 2.35)	(0.74, 2.48)	(0.77, 2.52)	(1.04, 3.26)	
Total myocardial infarction†	RR	1.0	1.16	1.01	1.27	1.42	.02
	(95% CI)	. . .	(0.83, 1.63)	(0.71, 1.44)	(0.91, 1.77)	(1.02, 1.98)	
	RR‡	1.0	1.16	1.04	1.32	1.48	.03
	(95% CI)	. . .	(0.82, 1.65)	(0.71, 1.51)	(0.91, 1.91)	(1.01, 2.16)	

CABG indicates coronary artery bypass graft; CHD, coronary heart disease; RR, relative risk; and CI, confidence intervals.
*Model includes age (7 categories); body mass (5 categories); smoking habits (current smoker [number of cigarettes smoked], former smoker, never smoked); alcohol consumption (4 categories); history of hypertension, diabetes, hypercholesterolemia; family history of myocardial infarction; profession; and quintiles of intake of total energy, vitamin E, total iron, heme iron.
†Includes nonfatal myocardial infarction and fatal CHD.
‡Further adjusted for quintile of intake of saturated fat and cholesterol.

TABLE 4. Relative Risk* of Myocardial Infarction (Fatal Coronary Heart Disease and Nonfatal Myocardial Infarction) According to Intake of Energy-Adjusted Heme Iron and Stratified by Selected Risk Factors for Coronary Disease

	Quintile of Heme Iron Intake					
	1	2	3	4	5	*P*, Trend
Use of vitamin E or multiple vitamin supplements						
Yes (n=20 444, cases=166)	1	1.09 (0.67, 1.77)	0.76 (0.44, 1.33)	0.86 (0.49, 1.49)	0.85 (0.48, 1.50)	.46
No (n=24 501, cases=220)	1	1.22 (0.73, 2.05)	1.36 (0.80, 2.31)	1.84 (1.09, 3.09)	2.17 (1.26, 3.74)	.002
Diabetes						
Yes (n=1141, cases=32)	1	2.93 (0.28, 31.0)	5.31 (0.52, 54.0)	4.00 (0.41, 39.1)	7.34 (0.75, 73.4)	.07
No (n=43 804, cases=354)	1	1.13 (0.79, 1.62)	0.98 (0.66, 1.44)	1.26 (0.86, 1.85)	1.36 (0.90, 2.04)	.12
Smoking habits						
Current or past smokers (n=24 272, cases=248)	1	1.32 (0.83, 2.11)	1.16 (0.70, 1.91)	1.63 (1.00, 2.66)	1.74 (1.04, 2.91)	.03
Never-smokers (n=20 673, cases=138)	1	1.01 (0.59, 1.72)	0.92 (0.52, 1.66)	0.97 (0.53, 1.78)	1.20 (0.63, 2.29)	.60
Hypercholesterolemia						
Yes (n=4702, cases=61)	1	3.08 (1.22, 7.76)	2.05 (0.71, 5.95)	3.08 (1.09, 0.87)	1.69 (0.51, 5.53)	.72
No (n=40 243, cases=325)	1	0.95 (0.64, 1.39)	0.92 (0.61, 1.38)	1.11 (0.74, 1.67)	1.38 (0.91, 2.11)	.05

*Adjusted for age (7 categories); body mass (5 categories); smoking habits (current smoker [number of cigarettes smoked], former smoker, never smoked); alcohol consumption (4 categories); history of hypertension; family history of myocardial infarction; profession; and quintiles of intake of total energy, vitamin E, total iron, total fat, saturated fat, polyunsaturated fat, *trans*-unsaturated fat, and cholesterol. Except when stratified by the specific risk factor, models were also adjusted for history of diabetes and hypercholesterolemia.

trans–fatty acids changed the point estimate of the relative risk only slightly (RR, 1.42; 95% CI, 0.96, 2.09; *P* for trend, .06).

The most plausible explanation for an effect of iron is by stimulating oxidation of low-density lipoprotein. We therefore explored whether intake of high doses of antioxidants or coronary risk factors that are believed to increase oxidative stress modify the association between heme iron intake and risk of myocardial infarction. Among the 24 501 men who did not report use of vitamin E or multiple vitamin supplements in the baseline questionnaire, the relative risk of myocardial infarction for the highest compared with the lowest quintile of heme iron intake was 2.17 (95% CI, 1.26, 3.74; *P* for trend, .002) (Table 4). The comparable relative risk among vitamin E or multiple vitamin users was 0.85 (95% CI, 0.48, 1.50; *P* for trend, .46). The difference in trend between users and nonusers of vitamins was statistically significant (*P*=.008). The relative risk of myocardial infarction for the highest versus the lowest quintile of heme iron intake was 7.34 (95% CI, 0.75, 73.4; *P* for trend, .07) among diabetics and 1.36 (95% CI, 0.90, 2.04; *P* for trend, .12) among nondiabetics. The difference in trend between diabetics and nondiabetics was not significant (*P*=.18). Also, the association between heme iron intake and risk of myocardial infarction was weaker—but not significantly weaker—among never-smokers compared with past and current smokers (Table 4). No clear differences in the association between heme iron intake and risk of myocardial infarction were observed in analyses stratified by history of hypercholesterolemia (Table 4). The association between heme iron intake and myocardial infarction was not changed by age or history of hypertension (data not shown).

To understand further this relation, we examined the contribution of individual food items to the differences in total heme iron intake in the study population. In stepwise regression with energy-adjusted heme iron as the dependent variable, beef, pork, or lamb as a main dish was the first variable to enter the model (R^2=.44). Other food items that contributed to heme iron intake were liver, beef in mixed dishes, hamburger, chicken, shrimp, and fish. After adjustment for standard risk factors, saturated fat, and cholesterol intake, the relative risk of myocardial infarction for men consuming beef four or more times per week compared with men consuming beef once per month or less was 1.38 (95% CI, 0.77, 2.29). A meat score—calculated as the sum in grams per day of beef (main dish or sandwich), hamburger, hot dog, chicken, liver, and other processed meat intake—was only weakly and not significantly associated with an increased risk of myocardial infarction; the relative risk for the top quintile (median intake, 145 g/d) compared with the bottom quintile (median intake, 16 g/d) was 1.18 (95% CI, 0.78, 1.80).

Discussion

In this large, prospective cohort study, we found no evidence for a positive association between total or nonheme iron intake and risk of coronary disease or myocardial infarction. Heme iron intake, largely from red meat, however, was positively associated with risk of myocardial infarction. This association was only partially accounted for by known risk factors for coronary disease and was stronger among men not taking vitamin E supplements.

Potential bias due to incomplete follow-up was minimized by the high follow-up rate. We also excluded from the analyses men with previous incidence of coronary heart disease who may have changed their diet as

a consequence of the disease. A previous diagnosis of hypercholesterolemia or diabetes may have caused a change in diet among some participants in the study, but such changes are unlikely to cause a direct association between heme iron intake and risk of myocardial infarction. Random error in the measurement of heme iron intake, however, has probably attenuated the observed relation.

Because of the positive correlation of heme iron intake with total dietary fat, saturated fat, and cholesterol, potential confounding by these variables was a major concern in our analyses. However, adjustment for these variables led to only a modest change in the estimated association between heme iron intake and risk of myocardial infarction. Also, among men in the cohort, about 67% of dietary saturated fat and 50% of dietary cholesterol are contributed by foods that do not contain appreciable amounts of heme iron; saturated fat and cholesterol jointly accounted for only 37% of the variation in heme iron intake. Thus, it was possible to estimate in multivariate analyses the association of heme iron with myocardial infarction independent of dietary fats.

There are several reasons to separate dietary heme iron from nonheme iron as potential risk factors for coronary disease. In men with replete iron stores, 26% of dietary heme iron is absorbed compared with only 2.5% of nonheme iron; in iron deficiency, heme absorption increased moderately to 47%, whereas nonheme iron absorption increased to 22%.[6] In addition, the availability of dietary nonheme iron is reduced or enhanced by several dietary factors. The efficient regulation of absorption of dietary nonheme iron and its variable bioavailability probably explain its lack of correlation with serum ferritin, an indicator of total iron stores. Also for these reasons, little association would be expected with risk of coronary heart disease in a generally well-nourished population of men.

In a prospective study among 1932 Finnish men, Salonen et al[4] found that serum ferritin and total iron intake were both strongly and positively associated with risk of myocardial infarction. The reported increase in risk of myocardial infarction was 5% for a 1-mg increase of daily iron intake. This association was adjusted for plasma levels of cholesterol but not for other dietary factors. The correlation between dietary iron and serum ferritin concentration was not reported. However, men in the Finnish study have a high meat intake,[15] and the reported association between dietary iron and risk of myocardial infarction probably reflects the predominant contribution of heme iron. Consistent with a positive association between heme iron intake and coronary risk is the 60% increased risk of fatal coronary disease among Seventh Day Adventists consuming meat at least six times per week compared with those consuming meat less than once per week.[16] No significant overall association between serum ferritin and myocardial infarction was found in a case control study nested in the Physicians' Health Study, a randomized trial on the effects of beta carotene and aspirin.[5] Baseline mean serum ferritin was 250 μg/L among the 238 men who had a myocardial infarction during the follow-up period and 220 μg/L in an equal number of matched control subjects (P=.08). A major difference between the Finnish men studied by Salonen and the physicians participating in the US study is their baseline risk of coronary disease. Finnish men had higher prevalence of smoking, diabetes, and hypercholesterolemia than US physicians. Also, half of the US physicians were taking high doses of beta carotene, which may have modified the effect of increased iron stores, and many were taking aspirin, which leads to bleeding from the gastrointestinal tract.

In our study, the association between heme iron intake and risk of myocardial infarction was limited to men who were not taking vitamin E or multiple vitamin supplements and was stronger among men with history of diabetes or smoking. High doses of vitamin E prevent lipid peroxidation,[17-20] whereas hyperglycemia[21-23] and cigarette smoking[24] increase lipoprotein oxidation. These results are consistent with the hypothesis that iron may adversely affect coronary risk only in the presence of oxidative stress from other sources. Free metal ions can catalyze the formation of the highly reactive hydroxyl radical from superoxide and hydrogen peroxide.[1] Whereas body iron is so tightly bound that there may not be free iron available in vivo under physiological conditions, oxidative stress can free iron from ferritin.[25,26] Thus, a preexisting oxidative stress may be required for the manifestation of the adverse effects linked to higher iron stores.

In addition to its possible chronic effect on lipid peroxidation and atherosclerosis, iron may be directly involved in the myocardial injury caused by ischemia and reperfusion. The results of animal experiments have shown that free radicals are generated after restoration of blood flow to ischemic myocardium[27,28] and contribute to the consequent myocardial injury.[29-31] A role of iron in causing myocardial damage in these animal models is supported by the protective effects of the iron chelator desferrioxamine.[32-36] Also, iron loading increased the risk of ventricular fibrillation and reduced contractility in rats exposed to anoxic and reperfusion conditions[37]; ventricular fibrillation was prevented and contractility was normalized by adding desferrioxamine or the antioxidant cyanidanol-3 to the perfusion of the iron-loaded animals.

The association of heme iron intake with risk of myocardial infarction and fatal coronary disease but not with risk of coronary bypass surgery suggests that high iron stores worsen the myocardial injury caused by ischemia rather than promoting atherosclerosis. An alternative, albeit less likely, explanation for the lack of association of heme iron with coronary surgery is the frequently elective nature of this procedure: Men with higher heme iron intake may be less willing to undergo surgery for coronary disease.

We also should consider the possibility that intake of heme iron increases the risk of myocardial infarction by mechanisms partly independent from its effects on total iron stores. Perhaps some heme iron is incorporated into chylomicrons or leaks into the intestinal lymph. In vitro, heme causes extensive oxidation of low-density lipoproteins.[38]

Finally, the observed association between heme iron intake and risk of myocardial infarction may be due to the adverse effect of some other unmeasured meat component. Because meat contributes almost all of dietary heme iron, we cannot exclude this possibility. However, heme iron intake had a stronger association

with risk of myocardial infarction than meat intake, making this hypothesis less likely.

Conclusions

Our results do not support the hypothesis that dietary iron in general increases the risk of coronary disease. They suggest, however, that high intake of heme iron is associated with an increased risk of myocardial infarction and are compatible with the possibility that increased iron stores may increase the risk of myocardial infarction. Our results also suggest that high intake of vitamin E may prevent the hypothetical adverse effect of heme iron, whereas diabetes and smoking may enhance it.

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References

1. Halliwell B. Current status review: free radicals, reactive oxygen species and human disease: a critical evaluation with special reference to atherosclerosis. *Br J Exp Pathol.* 1989;70:737-757.
2. McCord JM. Is iron sufficiency a risk factor in ischemic heart disease? *Circulation.* 1991;83:1112-1114.
3. Sullivan JL. The iron paradigm of ischemic heart disease. *Am Heart J.* 1989;117:1177-1188.
4. Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in Eastern Finnish men. *Circulation.* 1992; 86:803-811.
5. Stampfer MJ, Grodstein F, Rosenberg I, Willett WC, Hennekens CH. A prospective study of plasma ferritin and risk of myocardial infarction in US physicians. *Circulation.* 1993;87:10. Abstract.
6. Cook JD. Adaptation in iron metabolism. *Am J Clin Nutr.* 1990; 51:301-308.
7. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Ascherio A, Rosner B, Willett WC. A prospective study of alcohol consumption and the risk of coronary disease in men. *Lancet.* 1991; 338:464-468.
8. Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC. Dietary antioxidant intake and risk of coronary heart disease among men. *N Engl J Med.* 1993;328:1450-1456.
9. Rimm EB, Giovannucci E, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol.* 1992;135: 1114-1126.
10. Willett WC, Stampfer MJ. Total energy intake: implications for epidemiological analyses. *Am J Epidemiol.* 1986;124:17-27.
11. Beaton GH, Milner J, Corey P, McGuire V, Cousins M, Stewart E, de Ramos M, Hewitt D, Grambsch PV, Kassim N, Little JA. Sources of variance in 24-hour dietary recall data: implications for nutrition study design and interpretation. *Am J Clin Nutr.* 1979;32: 2546-2559.
12. Rose GA, Blackburn H. *Cardiovascular Survey Methods.* 2nd ed. Monograph series no. 58. World Health Organization, 1982.
13. Rothman KJ. *Modern Epidemiology.* Boston, Mass: Little, Brown & Co; 1986.
14. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. *J Am Stat Assoc.* 1963;58: 690-700.
15. Ihanainen M, Salonen R, Seppanen R, Salonen JT. Nutrition data collection in the Kuopio ischaemic heart disease risk factor study: nutrient intake of middle-aged Eastern Finnish men. *Nutr Res.* 1989;9:597-604.
16. Snowdon DA, Phillips RL, Fraser GA. Meat consumption and fatal ischemic heart disease. *Prev Med.* 1984;13:490-500.
17. Princen HMG, Poppek GV, Vogelzang C, Buytenhek R, Kok FJ. Supplementation with vitamin E but not β-carotene in vivo protects low density lipoprotein from lipid peroxidation in vitro: effect of cigarette smoking. *Arterioscler Thromb.* 1992;12:554-562.
18. Jialal I, Grundy SM. Effect of dietary supplementation with alpha-tocopherol on the oxidative modification of low density lipoprotein. *J Lipid Res.* 1992;33:899-906.
19. Dieber-Rothender M, Puhl M, Waeg G, Streigl G, Esterbauer H. Effect of oral supplementation with d-alpha-tocopherol on the vitamin E content of human LDL and resistance to oxidation. *J Lipid Res.* 1991;32:1325-1332.
20. Esterbauer H, Dieber-Rotheneder M, Striegl G, Waeg G. Role of vitamin E in preventing the oxidation of low-density lipoproteins. *Am J Clin Nutr.* 1991;53:314S-321S.
21. Chisolm GM, Kimberly CI, Penn MS. Lipoprotein oxidation and lipoprotein-induced cell injury in diabetes. *Diabetes.* 1992;(suppl 2): 61-66.
22. Hunt JV, Dean RT, Wolff SP. Hydroxyl radical production and autoxidative glycosilation. *Biochem J.* 1988;256:205-212.
23. Sakurai T, Sugioka K, Nakano M. O_2-generation and lipid peroxidation during the oxidation of a glycated polypeptide, glycated polylisine, in the presence of iron-ADP. *Biochim Biophys Acta.* 1990;1043:27-33.
24. Frei B, Forte TM, Ames BN, Cross CE. Gas phase oxidants of cigarette smoke induce lipid peroxidation and changes in lipoprotein properties in human blood plasma. *Biochem J.* 1991;277: 133-138.
25. Biemond P, Swaak AJ, Beindorff CM, Koster JF. Superoxide-dependent and -independent mechanisms of iron mobilization from ferritin by xanthine oxidase. *Biochem J.* 1986;239:169-173.
26. Koster JF, Slee RG. Ferritin, a physiological donor for microsomal lipid peroxidation. *FEBS Lett.* 1986;199:85-88.
27. Zweier JL, Flaherty JT, Weisfeldt ML. Direct measurement of free radical generation following reperfusion of ischemic myocardium. *Proc Natl Acad Sci U S A.* 1987;84:1404-1407.
28. Bolli R, Patel BS, Jeroudi MO, Lai EK, McCay PB. Demonstration of free radical generation in 'stunned' myocardium of intact dogs with the use of the spin trap alpha-phenyl *N-tert*-butyil nitrone. *J Clin Invest.* 1988;82:476-485.
29. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med.* 1985;312:159-163.
30. Ambrosio G, Weisfeldt ML, Jacobus WE, Flaherty JT. Evidence for a reversible oxygen radical-mediated component of reperfusion injury: reduction by recombinant human superoxide dismutase administered at the time of reflow. *Circulation.* 1987;75:282-291.
31. Bolli R, Zhu WX, Hartley CJ, Michael LH, Repine JE, Hess ML, Kukreja RC, Roberts R. Attenuation of disfunction in the post-ischemic 'stunned' myocardium by dimethylthiourea. *Circulation.* 1987;76:458-468.
32. Badylak SF, Simmons A, Turek J, Babbs CF. Protection from reperfusion injury in isolated rat heart by postischaemic deferoxamine and oxypurinol administration. *Cardiovasc Res.* 1987;21: 500-506.
33. Ambrosio G, Zweier JL, Jacobus WE, Weisfeldt ML, Flaherty JT. Improvement of postischemic myocardial function and metabolism induced by administration of deferoxamine at the time of reflow: the role of iron in the pathogenesis of reperfusion injury. *Circulation.* 1987;76:906-915.
34. Reddy BR, Kloner RA, Przyklenk K. Early treatment with deferoxamine limits myocardial ischemia/reperfusion injury. *Free Radic Biol Med.* 1989;7:45-52.
35. Lesnefsky EJ, Repine JE, Horwitz LD. Deferoxamine pretreatment reduces canine infarct size and oxidative injury. *J Pharmacol Exp Ther.* 1990;253:1103-1109.
36. Bernier M, Hearse DJ, Manning AS. Reperfusion-induced arrhythmias and oxygen-derived free radicals. *Circ Res.* 1986;58: 331-340.
37. Van der Kraaj AMM, Mostert LJ, van Eijk HG, Koster JF. Iron load increases the susceptibility of rat hearts to oxygen reperfusion damage. *Circulation.* 1988;78:442-449.
38. Balla G, Jacob HS, Eaton JW, Belcher JD, Vercellotti GM. Hemin: a possible physiological mediator of low density lipoprotein oxidation and endothelial injury. *Arterioscler Thromb.* 1991;11:1700-1711.

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