Heme Iron From Diet as a Risk Factor for Coronary Heart Disease in Women With Type 2 Diabetes

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OBJECTIVE — Diabetes-related metabolic abnormality may aggravate the adverse effects of iron overload on cardiovascular health. However, little is known about whether iron consumption affects coronary heart disease (CHD) risk in diabetes.

RESEARCH DESIGN AND METHODS — We prospectively assessed the associations of long-term intakes of dietary iron and red meat with CHD risk among 6,161 women who reported a diagnosis of type 2 diabetes.

RESULTS — During 54,455 person-years of follow-up from 1980 through 2000, we documented 550 incident cases of CHD. After adjustment for age and BMI, high intakes of both heme iron and red meat were associated with a significantly increased risk of fatal CHD (P for trend = 0.003 and 0.018), coronary revascularization (P for trend = 0.02 and 0.06), and total CHD (P for trend = 0.0009 and 0.007). Women with the highest intake of heme iron had 50% (6–94%) increased risk of total CHD compared with those with the lowest intake. Further adjustment for other lifestyle and dietary factors did not appreciably change the associations. The positive association between heme iron and red meat intakes and CHD was more evident among postmenopausal women compared with premenopausal women.

CONCLUSIONS — Our data indicate that higher consumption of heme iron and red meat may increase CHD risk among women with type 2 diabetes.

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Excess body iron can impose oxidative injury that is associated with several cardiovascular risk factors including dyslipidemia, insulin resistance, and inflammation (1,2) and may contribute to the development of atherosclerosis. Iron overload has been linked in some studies to increased risks of ischemic heart disease, although these associations remain controversial (3–6).

Iron homeostasis is primarily controlled by intestinal absorption (7). Body iron stores accumulate by increasing absorption of dietary iron (heme and nonheme) and act as a regulator in preventing excessive absorption (8). Compared with heme iron, absorption of nonheme iron is more likely to be influenced by other dietary factors such as vitamin C and alcohol (9,10). The genetic variability may also affect iron absorption (10,11). Intake of dietary iron, especially highly bioavailable heme iron, was recently associated with greater risk of type 2 diabetes (12,13), coronary heart disease (CHD), and cardiovascular mortality among nondiabetic women (14,15). Complications of atherosclerosis cause most morbidity and mortality in patients with diabetes (16). Diabetes is associated with high levels of body iron (17) and a constellation of metabolic abnormalities (16). Earlier evidence suggested that diabetes status may exacerbate the proatherosclerotic effects of iron overload (4,18,19). However, data on the relation between iron intakes and coronary risk in diabetic patients are sparse.

In the present study, we prospectively examined the long-term consumption of dietary iron and its major food source, red meat, in relation to the incidence of CHD among women with type 2 diabetes from the Nurses' Health Study.

RESEARCH DESIGN AND METHODS

— The Nurses' Health Study cohort was established in 1976 when 121,700 female registered nurses, 30–55 years old and residing in 11 large U.S. states completed a mailed questionnaire about their medical history and lifestyle. Every 2 years, follow-up questionnaires have been sent to update information on potential risk factors and to identify newly diagnosed cases of CHD and other illness (20). The present investigation included 6,161 women who reported a physician diagnosis of type 2 diabetes at 30 years of age, from baseline through 2000. Women with a history of CHD (including myocardial infarction, angina, and/or coronary revascularization), stroke, or cancer reported on the 1980 questionnaire (when diet was first assessed), or before, were excluded at baseline.

Confirmation of diabetes

A supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy was mailed to women who indicated on any biennial questionnaire that they had diabetes. We used National Diabetes Data Group criteria to define diabetes because diabetes in our subjects was diagnosed before the release of the American Diabetes Association criteria in 1997 (21). The validity of this method has been confirmed (22). We used the American Diabetes Association diagnostic criteria for diabetes during the 1998 and 2000 cycles. A woman was considered to have diabetes if at least one of the follow-

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Abbreviations: CHD, coronary heart disease; FFQ, food frequency questionnaire.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Age-standardized baseline characteristics according to quintiles of heme iron and red meat*

	Heme iron (mg/day)				Red meat (servings/day)			
	Q1	Q3	Q5	*P* value*	Q1	Q3	Q5	*P* value*
Median intake	1.70	2.23	2.83		0.55	1.22	2.39	
Age (years)	48	49	49	0.69	49	49	48	<0.01
BMI (kg/m^2)	28.0	29.1	28.5	0.22	27.5	27.5	29.2	<0.01
Current smoking (%)	26.5	23.4	29.7	0.37	23.9	30.5	26.1	0.49
Alcohol consumption (g/day)	3.9	2.5	3.4	0.14	3.3	3.9	3.0	0.11
Physical activity (h/week)	3.3	3.4	3.4	0.97	3.8	3.4	3.0	<0.01
Family history of myocardial infarction (%)	24.7	22.9	25.7	0.53	20.9	23.5	25.4	0.11
History of hypertension (%)	43.9	50.6	55.6	0.08	42.5	47.9	44.5	0.08
History of hypercholesterolemia (%)	16.2	25.2	14.2	0.15	19.5	15.8	15.7	0.31
Current estrogen therapy among postmenopausal women	17.1	24.1	20.3	0.23	12.1	14.3	17.5	0.06
Current aspirin use (%)	40.0	33.7	37.1	0.39	35.7	37.3	39.8	0.66
Duration of diabetes (years)	8.0	7.1	8.2	0.73	8.3	8.8	8.1	0.32
Diet								
Saturated fat (% of energy)	14.9	17.9	19.8	<0.01	12.4	15.5	18.3	<0.01
Polyunsaturated fat (% of energy)	5.3	5.3	5.1	0.56	4.9	5.0	5.5	<0.01
PS ratio	0.37	0.30	0.27	<0.01	0.42	0.33	0.31	<0.01
Trans fat (% of energy)	2.1	2.5	2.4	<0.01	1.7	2.1	2.5	<0.01
Cereal fiber (g/day)	2.7	2.2	1.4	<0.01	3.0	2.6	2.2	<0.01
Dietary glycemic load	89	68	51	<0.01	96	84	71	<0.01
Vitamin C (mg/day)	347	269	275	0.08	481	331	245	<0.01

*Test for trend for continuous variables. PS ratio, ratio of polyunsaturated fat to saturated fat; Q, quintile.

ing was present: *1*) classic symptoms plus elevated fasting plasma glucose ≥7.8 mmol/l, and/or random plasma glucose ≥11.1 mmol/l, and/or plasma glucose ≥11.1 mmol/l after ≥2 h during an oral glucose tolerance test; *2*) no symptoms but at least two elevated plasma glucose concentrations (by the above criteria) on different occasions; or *3*) treatment with oral hypoglycemic agents or insulin.

CHD ascertainment

The end points of CHD consisted of fatal CHD, nonfatal myocardial infarction, and coronary revascularization (coronary bypass surgery or coronary angioplasty). Angina pectoris was not included. Nonfatal myocardial infarction was confirmed by reviewing medical records using the criteria of the World Health Organization of symptoms plus either typical electrocardiographic changes or elevated cardiac enzyme levels. Fatal CHD were confirmed by review of medical records or autopsy reports with the permission of the next of kin or if CHD was listed as the cause of death on the death certificate, if it was the underlying and most plausible cause, and if evidence of previous CHD was available (by questionnaire or per next of kin). Sudden deaths (i.e., death within 1 h of symptom onset without known disease that could explain death) were considered to be due to cardiovascular causes. The records were reviewed by physicians blinded to the self-reported risk factor status. Patients with CHD that was diagnosed before the diagnosis of diabetes were excluded.

Assessment of dietary intakes

Detailed dietary information was obtained through the use of semiquantitative food frequency questionnaires (FFQs). Participants were asked to report their average frequency of consumption of selected foods and beverages with a specified commonly used unit or portion size during the previous year. The reproducibility and validity of the dietary questionnaires were assessed by comparing nutrient intake from the FFQ with two 1-week diet records spaced 6 months apart (23). The correlation coefficient for energy-adjusted total dietary iron intake was 0.60 after adjustment for within-person variability in daily intake. Dietary heme iron was found to be a significant predictor of body iron stores in our cohort (24).

Statistical analyses

Person-months of follow-up accumulated starting with the return of the 1980 questionnaire. Participants who had a diagnosis of CHD or died during follow-up were censored at the date of diagnosis or death. All other participants were followed through January 2000 or the return date of the last questionnaire if no questionnaire was returned in 2000. To better estimate long-term effect, we used the updated cumulative average from all available dietary questionnaires up to the start of each 2-year follow-up interval in which events were reported (1980, 1984, 1986, 1990, 1994, and 1998) for intakes of iron, red meat (beef, pork, or lamb as a main dish; beef as a sandwich or mixed dish; hamburger; hot dog; processed meat; and bacon), and other nutrients (25).

We divided women into quintiles of intakes and calculated incidence rates in each quintile. The relative risk (RR) was computed in a specific quintile compared with the lowest quintile, with adjustment for age in 5-year categories and BMI. In multivariate analyses using Cox proportional hazards analysis, cigarette smoking, alcohol use, history of hypertension and high cholesterol, family history of CHD, physical activity, aspirin use, duration of diabetes, menopausal status and postmenopausal hormone use, dietary factors (cereal fiber, trans fat, the ratio of polyunsaturated to saturated fats, glycemic load, and vitamin C) were additionally adjusted. The SAS statistical package

Table 2—*RR for CHD according to the intakes of total iron and heme iron*

	RR (95% CI) according to intakes					
	Q1	Q2	Q3	Q4	Q5	*P* for trend
Total iron intake						
Person-years	10,922	10,880	10,907	10,835	10,911	
Nonfatal myocardial infarction	58	53	41	48	59	
Age and BMI adjusted	1.0	0.83 (0.56–1.23)	0.63 (0.41–0.97)	0.75 (0.49–1.14)	0.92 (0.62–1.37)	0.66
Multivariate	1.0	0.80 (0.53–1.21)	0.64 (0.40–1.02)	0.79 (0.50–1.27)	1.09 (0.69–1.72)	0.11
Fatal CHD	20	40	29	28	36	
Age and BMI adjusted	1.0	1.54 (0.88–2.69)	1.06 (0.58–1.92)	1.02 (0.56–1.87)	1.30 (0.73–2.31)	0.78
Multivariate	1.0	1.86 (1.04–3.33)	1.57 (0.82–3.01)	1.60 (0.82–3.11)	2.10 (1.11–3.98)	0.10
Coronary revascularization	14	27	33	37	27	
Age and BMI adjusted	1.0	1.42 (0.73–2.77)	1.54 (0.80–2.97)	1.76 (0.92–3.36)	1.30 (0.66–2.54)	0.97
Multivariate	1.0	1.31 (0.65–2.62)	1.52 (0.75–3.10)	1.90 (0.92–3.92)	1.47 (0.69–3.13)	0.64
Total CHD	92	120	103	113	122	
Age and BMI adjusted	1.0	1.09 (0.82–1.45)	0.89 (0.66–1.20)	0.99 (0.73–1.33)	1.06 (0.80–1.42)	0.64
Multivariate	1.0	1.10 (0.82–1.49)	0.98 (0.71–1.36)	1.15 (0.82–1.59)	1.32 (0.95–1.84)	0.04
Heme iron intake						
Person-years	11,186	10,830	10,748	10,539	11,152	
Nonfatal myocardial infarction	47	57	42	54	59	
Age and BMI adjusted	1.0	1.28 (0.84–1.95)	0.94 (0.60–1.48)	1.20 (0.78–1.85)	1.27 (0.83–1.94)	0.35
Multivariate	1.0	1.21 (0.79–1.86)	0.87 (0.54−1.39)	1.10 (0.69–1.75)	1.22 (0.74–2.00)	0.51
Fatal CHD	20	24	24	44	41	
Age and BMI adjusted	1.0	1.00 (0.54–1.85)	1.02 (0.55–1.89)	1.87 (1.07–3.28)	1.78 (1.01–3.15)	0.003
Multivariate	1.0	1.06 (0.56–2.00)	1.00 (0.52–1.89)	1.78 (0.96–3.30)	1.64 (0.85–3.17)	0.04
Coronary revascularization	16	22	31	33	36	
Age and BMI adjusted	1.0	1.00 (0.51–1.95)	1.42 (0.76–2.67)	1.48 (0.79–2.78)	1.74 (0.93–3.23)	0.02
Multivariate	1.0	0.95 (0.48–1.87)	1.32 (0.68–2.57)	1.51 (0.76–2.99)	1.79 (0.87–3.70)	0.04
Total CHD	83	103	97	131	136	
Age and BMI adjusted	1.0	1.13 (0.83–1.54)	1.07 (0.78–1.46)	1.44 (1.06–1.94)	1.50 (1.06–1.94)	0.0009
Multivariate	1.0	1.09 (0.80–1.50)	1.03 (0.76–1.40)	1.35 (0.97–1.86)	1.43 (1.01–2.01)	0.01

Multivariate values adjusted for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, duration of diabetes, history of hypertension and hypercholesterolemia, postmenopausal hormone use, family history of CHD, cereal fiber, glycemic load, polyunsaturated fat–to–saturated fat ratio, trans fat, multivitamin use, and vitamin C. Q, quintile.

Table 3—*RR for CHD according to the intakes of red meat*

	RR (95% CI) according to intakes					
	Q1	Q2	Q3	Q4	Q5	*P* for trend
Person-years	11,046	10,948	10,829	10,785	10,847	
Nonfatal myocardial infarction	56	50	48	49	56	
Age and BMI adjusted	1.0	0.93 (0.63–1.36)	0.92 (0.62–1.36)	0.98 (0.66–1.44)	1.12 (0.77–1.63)	0.44
Multivariate	1.0	0.82 (0.55–1.22)	0.79 (0.52–1.20)	0.83 (0.53–1.30)	0.91 (0.56–1.47)	0.95
Fatal CHD	26	33	29	27	38	
Age and BMI adjusted	1.0	1.35 (0.80–2.25)	1.29 (0.76–2.20)	1.28 (0.74–2.20)	1.91 (1.15–3.16)	0.018
Multivariate	1.0	1.40 (0.82–2.40)	1.35 (0.76–2.40)	1.45 (0.78–2.68)	2.05 (1.08–3.90)	0.039
Coronary revascularization	26	24	27	31	30	
Age and BMI adjusted	1.0	0.95 (0.55–1.66)	1.08 (0.63–1.87)	1.38 (0.81–2.32)	1.47 (0.86–2.51)	0.06
Multivariate	1.0	0.93 (0.54–1.75)	1.22 (0.67–2.22)	1.66 (0.89–3.09)	1.91 (0.96–3.83)	0.02
Total CHD	108	107	104	107	124	
Age and BMI adjusted	1.0	1.03 (0.79–1.35)	1.05 (0.80–1.37)	1.15 (0.88–1.50)	1.38 (1.06–1.80)	0.007
Multivariate	1.0	0.99 (0.75–1.31)	1.01 (0.76–1.37)	1.15 (0.84–1.57)	1.36 (0.97–1.91)	0.03

Multivariate analysis adjusted for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, duration of diabetes, history of hypertension and hypercholesterolemia, postmenopausal hormone use, family history of CHD, cereal fiber, glycemic load, polyunsaturated fat–to–saturated fat ratio, trans fat, multivitamin use, and vitamin C.

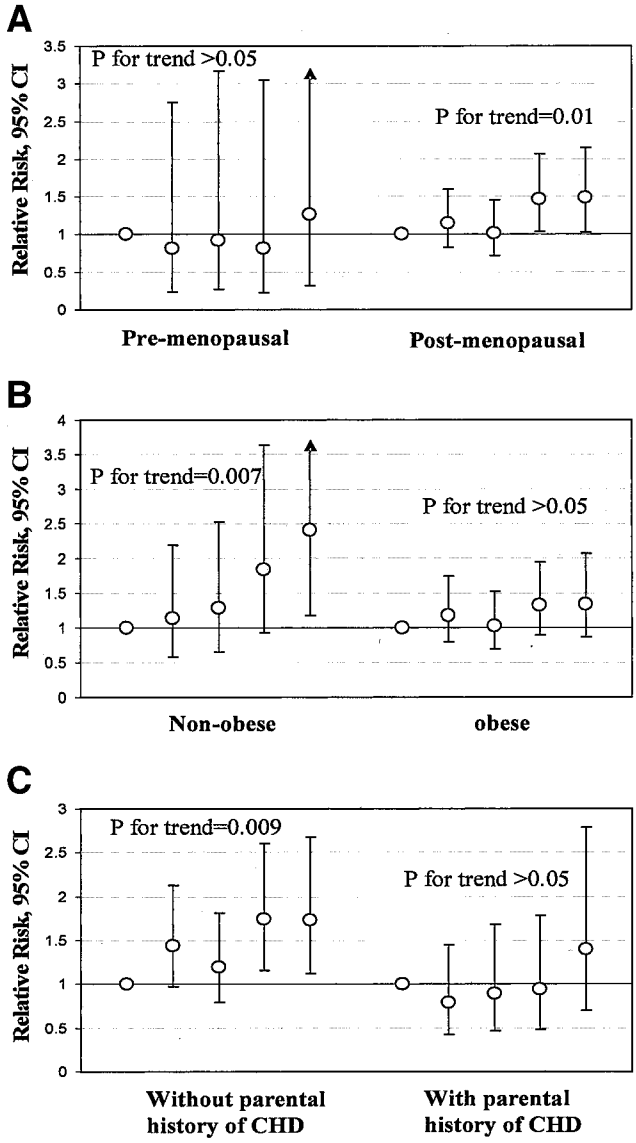

Figure 1—*The adjusted associations of heme iron intake (in quintiles) with CHD in diabetic women by menopausal status* (A)*, obese status (cutoff 30 kg/m*^{2}) (B)*, and parental history of CHD* (C)*. The RR and 95% CI are presented. Analyses were adjusted for age, BMI, smoking, alcohol consumption, physical activity, aspirin use, duration of diabetes, history of hypertension and hypercholesterolemia, postmenopausal hormone use, family history of CHD, cereal fiber, glycemic load, polyunsaturated fat–to–saturated fat ratio, trans fat, multivitamin use, and vitamin C.*

(version 8.2 for UNIX) was used for the analyses. All *P* values were two sided. $P \leq 0.05$ was considered statistically significant.

RESULTS — During 54,455 person-years of follow-up from 1980 to 2000, we ascertained 550 incident cases of CHD (259 nonfatal myocardial infarctions, 153 CHD deaths, and 138 bypass operations or angioplasties). At baseline, women in the highest quintile of heme iron intake were more likely to have hypertension compared with those in the lowest quintile (Table 1). High heme iron and red meat intakes were associated with high intakes of saturated fat, low intakes of cereal fiber and vitamin C, and low dietary glycemic load.

After adjustment for age and BMI, high intake of heme iron was significantly associated with higher risk of fatal CHD, coronary revascularization, and total CHD (Table 2). Women with the highest intake of heme iron had 50% (6–94%) increased risk of total CHD compared with those with the lowest intake. Further adjustment for other covariates did not significantly change the associations. Consumption of total iron was associated with a marginally increasing trend of total CHD risk only in the multivariate analyses. Intake of red meat was also associated with significantly increased risk of fatal CHD, coronary revascularization, and total CHD, independent of age, BMI, and other covariates (Table 3).

In the subgroup analyses, the associations of heme iron intake and total CHD appeared to be stronger among the postmenopausal women than among the premenopausal women (Fig. 1). In addition, the associations of heme iron with CHD were stronger among nonobese women or those who did not have a family history of CHD, although tests for interactions were not significant. An earlier study suggested that alcohol consumption may strengthen the association between heme iron intake and CVD mortality (15). Our stratified analyses by alcohol consumption (cutoff 5 g/day) did not confirm this interaction. The associations between red meat intakes and CHD showed similar patterns in the subgroup analyses.

CONCLUSIONS — Patients with type 2 diabetes are at high risk for subsequent CHD (16). In this prospective cohort study of diabetic women, we found that intakes of dietary iron, especially heme iron and red meat, were significantly associated with a greater risk of fatal CHD, coronary revascularization, and total CHD. The observed associations were independent of conventional risk factors for CHD.

Little is known about the effects of dietary iron on cardiovascular risk in diabetes. Our findings that high intake of heme iron was associated with greater CHD risk among diabetic women are consistent with recent observations in nondiabetic women, in whom a relatively high heme iron intake was associated with significantly increased risk of CHD (14). In the Iowa Women's Health Study, Lee et al. (15) found that dietary heme iron intake was associated with greater cardiovascular mortality in women with high alcohol consumption. The associations between heme iron intake and increased cardiovascular events were also observed in other studies (26,27). Diabetes-related metabolic abnormalities such as dyslipidemia may strengthen the detrimental effects of iron overload (18,19). Our data indicate that high consumption of iron, especially heme iron, may increase CHD risk in diabetes.

Intestinal absorption of dietary iron plays a determinant role in body iron homeostasis. Iron consumed in the diet is

either heme iron or nonheme iron. Heme iron is found mainly in red meats, poultry, and seafood. Nonheme iron is found in both plant and animal foods. Heme iron is highly bioavailable because of its ability to circumvent the downregulation mechanism of nonheme iron absorption in iron overload and contributes substantially to the total iron from the typical U.S. diet (28,29). Compared with total iron (heme and nonheme) intake, heme iron has been more consistently associated with increased risk of CHD and cardiovascular mortality (14,15,26,27,30,31). The associations between heme iron and CHD risk appear to be more marked in postmenopausal women. Premenopausal women may lose a significant amount of iron during menstruation, which may dilute the relationship between iron intake and CHD risk. In this study, we also found that red meat, the major food source of heme iron, was associated with an increasing trend of CHD risk. These finding are consistent with our earlier observation in nondiabetic women (32). Because other components in red meat such as saturated fat may also affect coronary health, it is difficult to tease out the independent effects of each component.

Several limitations of the present study warrant consideration. We could not completely exclude the possibilities of residual confounding because of imperfect measures of diet and lifestyle factors. For example, heme iron is correlated with saturated fat. Both heme iron and saturated fat are measured with errors in the dietary questionnaire; residual confounding by saturated fat is unavoidable even after careful adjustment. Because diabetes is self-reported and confirmed by a supplemental questionnaire, there is a potential for misclassification of disease status and self-reported duration of diabetes. However, the supplementary questionnaire used for diabetes diagnosis has been shown to be valid on the basis of medical record review (22). As an advantage, the dietary variables were assessed repeatedly, and iron intake assessed by the FFQ was validated against diet records (23). Such data not only represent long-term intake but also minimize the measurement error.

In summary, we found significant associations between intakes of heme iron and red meat and CHD risk among diabetic women. Whether the increased iron intake is causally related to increased risk in CHD remains to be proven. These findings suggest that patients with type 2 diabetes may consider reducing their consumption of heme iron and red meat for the prevention of CHD.

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