Dietary iron intake and blood donations in relation to risk of type 2 diabetes in men: a prospective cohort study[1–3]

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ABSTRACT

Background: Excessive iron stores may promote insulin resistance and lead to the development of type 2 diabetes. However, prospective data relating iron intake and blood donations (determinants of body iron stores) to diabetes incidence are limited.

Objective: We examined iron intake and blood donations in relation to the incidence of type 2 diabetes.

Design: We followed men aged 40–75 y who participated in the Health Professionals' Follow-up Study; were free of diabetes, cardiovascular disease, and cancer in 1986; and provided dietary data ($n = 38\,394$). Of those participants, 33 541 also provided a history of blood donation during the past 30 y in 1992.

Results: During 12 y of follow-up, we ascertained 1168 new cases of type 2 diabetes. After adjustment for age, body mass index, and other diabetes risk factors, total iron intake was not associated with the risk of type 2 diabetes. Intakes of total heme iron [multivariate relative risk (RR) for extreme quintiles: 1.28; 95% CI: 1.02, 1.61; P for trend = 0.045] and of heme iron from red meat (RR: 1.63; 1.26, 2.10; P for trend < 0.001) were associated with an increased risk. However, heme-iron intake from sources other than red meat was not associated with diabetes risk (RR: 0.99; 0.81, 1.22). No significant associations were found between blood donation and the risk of type 2 diabetes.

Conclusions: Heme-iron intake from red meat sources is positively associated with the risk of type 2 diabetes. Total iron intake, heme-iron intake from non–red meat sources, and blood donations are not related to the risk of type 2 diabetes. *Am J Clin Nutr* 2004;79:70–5.

KEY WORDS Dietary iron, heme iron, blood donation, type 2 diabetes, men, Health Professionals' Follow-up Study

INTRODUCTION

Type 2 diabetes is a common manifestation of hemochromatosis, a disease of massive iron overload (1), which has led to speculation that high iron stores may increase the risk of developing type 2 diabetes. Iron is a redox-active transitional metal that can catalyze the formation of hydroxyl radicals, which are powerful prooxidants (2) that have been implicated in the etiology of diabetes (3, 4). A prospective, nested case-control study in Finland suggested a positive association between iron stores (assessed by using the ratio of 2 biomarkers of iron stores: serum transferrin receptor concentration and serum ferritin concentration) and the incidence of diabetes in a healthy population (5). Several cross-sectional and case-control studies observed positive associations between serum ferritin concentration and insulin resistance (6–9) or the risk of diabetes (10, 11). However, serum ferritin concentrations are not entirely specific for body iron stores and may reflect other mechanisms, such as inflammation, that are related to insulin resistance. A recent study showed that, compared with meat eaters (meat is a major source of heme iron), lactoovovegetarians had lower serum ferritin concentrations and were more insulin sensitive (12), but the difference in insulin sensitivity could be explained by differences in other components of diet and lifestyle between lactoovovegetarians and meat eaters. Thus, although iron stores that are elevated but lower than those associated with hemochromatosis might predict the development of type 2 diabetes (5), epidemiologic evidence supporting the hypothesis is limited. Dietary iron (especially highly bioavailable heme iron) is the major source of body iron stores, which accumulate almost linearly with age in men (13), and blood donation effectively reduces iron stores (14). Therefore, we prospectively examined dietary iron intake and history of blood donations in relation to the incidence of type 2 diabetes in a large cohort of men.

SUBJECTS AND METHODS

Health Professionals' Follow-up Study

The Health Professionals' Follow-up Study is a prospective investigation designed to study the etiologies of heart disease, cancer, and other major diseases. In 1986, 51 529 male health professionals who were 40–75 y of age and from all 50 states completed a detailed mailed questionnaire on medical history, diet, and other potential risk factors for major diseases. Updated information on disease status and health behaviors was collected on biennially mailed questionnaires, and diet was assessed every 4 y by using semiquantitative food-frequency questionnaires. In the present study, we excluded men with

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inadequate assessment of diet [questions on ≥70 food items left blank or with implausibly high (>4200 kcal/d) or low (<800 kcal/d) total energy intake]. We also excluded men with a history of diabetes, cardiovascular disease (angina, coronary bypass or angioplasty, myocardial infarction, and stroke), or cancer (except for nonmelanoma skin cancer) at baseline because diagnosis of these conditions can lead to changes in diet and lifestyle. After these exclusions, 38 394 participants remained. The study was approved by the Brigham and Women's Hospital Human Subjects Committee.

Dietary assessment

In addition to containing questions on 131 food items with a specified, commonly used unit or portion size, the semiquantitative food-frequency questionnaire included an open-ended section for foods not listed (15). Participants were asked to report how often, on average, during the previous year they had consumed selected foods and beverages. Nine responses were included, which ranged from "never" to "≥6 times/d." Nutrient intakes were computed by multiplying the consumption frequency of each food by the nutrient content of the specified portion and then summing these products for all the food items. The food-composition values were obtained from the Harvard University Food Composition Database, which is derived from US Department of Agriculture sources (16) and was supplemented with manufacturers' information. In a validation study of the food-frequency questionnaire in a random sample of 127 men from this cohort, the Pearson correlation coefficient between total iron intake assessed by using the 1986 questionnaire and total iron intake assessed by using two 1-wk dietary records obtained ≈7 mo apart (17) was 0.54.

Assessment of blood donations

In 1992 we asked the participants to report their total number of blood donations during the past 30 y. Eight responses were included: never, ≤5, 6–9, 10–19, 20–29, 30–59, 60–89, and ≥90. The reported number of blood donations was validated by serum ferritin concentrations. We measured serum ferritin concentrations in a random sample of 123 men in the cohort, and the blood samples for the validation study were collected in 1986. Because only a few of the men had >30 blood donations, we grouped them into one category (≥30). The mean serum ferritin concentrations for the 6 categories of blood donations (ie, never, ≤5, 6–9, 10–19, 20–29, and ≥30) were 187, 186, 187, 160, 93, and 64 μg/L, respectively (18).

Measurement of nondietary risk factors for diabetes

Participants reported their body weight, cigarette smoking, and leisure-time physical activity every 2 y during the follow-up. The correlation coefficient between self-reported weight and measured weight was 0.96 (19). Physical activity (in metabolic equivalent · h/wk) was estimated on the basis of the reported time spent doing various activities (each activity was weighted by its intensity level) (20). The validity of self-reported physical activity in this cohort was reported previously (20). In 1987 and 1990, the participants provided information on the history of diabetes in their first-degree relatives.

Outcome ascertainment

We mailed a supplementary questionnaire regarding diabetes symptoms, diagnostic tests, and treatments to all participants who reported a diagnosis of diabetes on any biennial follow-up questionnaire. Confirmed diabetes cases were documented by using the supplementary questionnaire. Subjects were confirmed as having diabetes if they met at least one of the following criteria: *1*) at least one classic symptom (excessive thirst, polyuria, weight loss, hunger, or coma) plus a fasting plasma glucose concentration ≥ 140 mg/dL (7.8 mmol/L) or a random plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L), *2*) elevated plasma glucose concentrations on ≥2 occasions (a fasting plasma glucose concentration ≥ 140 mg/dL, a random plasma glucose concentration ≥ 200 mg/dL, or a random plasma glucose concentration ≥ 200 mg/dL after ≥2 h of oral-glucose-tolerance testing) in the absence of symptoms, or *3*) treatment with hypoglycemic medication (insulin or oral hypoglycemic agents). The diagnostic criteria for type 2 diabetes were changed in 1997 (21), but we used the criteria proposed earlier by the National Diabetes Data Group (22) because most of our cases were diagnosed before 1997. Men with type 1 diabetes were excluded. A validation study in a random sample of this cohort showed that our supplementary questionnaire is highly accurate in confirming diabetes diagnoses. Of 71 men classified as having type 2 diabetes according to the information reported on the supplementary questionnaire, medical records were available for 59. A physician who was blinded to the information reported on the questionnaire reviewed the records, and the diagnosis of type 2 diabetes was confirmed in 57 of the 59 men (97%) (23).

Data analysis

Each participant contributed follow-up time from the date of returning the 1986 questionnaire (in the analysis of the association between iron intake and diabetes incidence) or the 1992 questionnaire (in the analysis of the association between blood donations and diabetes incidence) to the date of first diagnosis of type 2 diabetes, death, or 1 June 1998, whichever came first. To reduce within-subject variation and best represent long-term dietary intake, we used repeated measures of diet in the analyses. In the analyses, the incidence of type 2 diabetes was related to the cumulative average iron intake from all available questionnaires up to the start of each 2-y follow-up interval (24). For example, the incidence of diabetes during the 1986–1990 time period was related to iron intake from the 1986 questionnaire, and the incidence of diabetes during the 1990–1994 time period was related to the average iron intake from the 1986 and 1990 questionnaires. We stopped updating dietary intake for men who developed cardiovascular disease because subsequent changes in diet could confound the relation between diet and diabetes. The incidence of type 2 diabetes was also related to the number of blood donations reported in 1992.

Relative risks of diabetes were calculated from Cox proportional hazards models (25, 26). To test the proportional hazards assumption, we conducted likelihood ratio tests by comparing nested models with and without product interaction terms for the interaction between categories of exposure and follow-up time. None of the tests were statistically significant, which indicated that the hazard ratio for the exposures could be assured of being reasonably constant over time. We excluded men from subsequent follow-up if they developed diabetes. In multivariate models, we adjusted for age, body mass index (BMI; in kg/m^2), family history of diabetes, physical activity, smoking, alcohol consumption, and dietary variables, including

TABLE 1

Age-adjusted potential risk factors for type 2 diabetes according to quintiles (Qs) of energy-adjusted total iron and heme-iron intake and categories of lifetime number of blood donations at baseline in 1986[1]

	Total iron intake		Heme-iron intake		No. of blood donations	
Variable	Q1 (*n* = 7751)	Q5 (*n* = 7503)	Q1 (*n* = 8760)	Q5 (*n* = 7234)	0 (*n* = 13 835)	≥30 (*n* = 1605)
Age (y)	52.4 ± 9.4[2]	54.2 ± 9.4	53.3 ± 9.7	53.0 ± 9.0	59.3 ± 9.5	58.2 ± 8.2
BMI (kg/m^2)	25.6 ± 3.2	25.1 ± 3.0	24.8 ± 3.0	26.2 ± 3.6	25.7 ± 3.5	26.2 ± 3.6
Family history of diabetes (%)	12.7	13.0	12.9	12.7	12.1	15.5
Physical activity (MET · h/wk)	19.5 ± 27.0	24.1 ± 33.6	26.0 ± 33.4	17.6 ± 26.3	36.6 ± 43.7	39.1 ± 41.4
Current smoker (%)	13.8	8.2	6.7	12.7	8.0	5.6
Alcohol consumption (g/d)	15.0 ± 19.1	10.2 ± 14.1	10.9 ± 15.9	10.1 ± 13.6	10.7 ± 14.6	10.6 ± 14.1
Multivitamin use (%)	26.1	79.0	46.5	38.0	29.1	40.6
Diet						
Fat intake (% of energy)						
Polyunsaturated	5.9 ± 1.8	5.9 ± 1.6	5.9 ± 1.9	5.9 ± 1.4	5.9 ± 1.4	5.9 ± 1.3
Saturated	11.7 ± 2.9	10.4 ± 2.8	9.6 ± 2.9	12.6 ± 2.4	10.7 ± 2.6	11.0 ± 2.3
trans	1.33 ± 0.53	1.16 ± 0.50	1.13 ± 0.56	1.37 ± 0.44	1.35 ± 0.51	1.41 ± 0.46
Cereal fiber intake (g/d)	3.9 ± 2.1	7.2 ± 5.7	7.2 ± 4.8	4.5 ± 3.1	6.1 ± 3.6	6.4 ± 3.4
Magnesium intake (mg/d)	305 ± 60.7	415 ± 103	381 ± 97.0	328 ± 73.3	359 ± 81.1	364 ± 71.2
Glycemic load	170 ± 39.4	183 ± 38.4	202 ± 38.6	150 ± 29.9	182 ± 35.4	179 ± 31.0
Whole-grain intake (servings · d^{-1} · 1000 kcal^{-1})	0.46 ± 0.47	0.97 ± 0.78	1.02 ± 0.85	0.55 ± 0.50	0.65 ± 0.54	0.67 ± 0.51
Vegetable intake (servings · d^{-1} · 1000 kcal^{-1})[3]	1.23 ± 0.63	1.70 ± 0.95	1.64 ± 0.96	1.54 ± 0.82	1.70 ± 0.88	1.66 ± 0.83
Fruit intake (servings · d^{-1} · 1000 kcal^{-1})[4]	1.08 ± 0.79	1.32 ± 0.79	1.49 ± 0.90	0.93 ± 0.61	1.21 ± 0.72	1.18 ± 0.63
Red meat intake (servings · d^{-1} · 1000 kcal^{-1})[5]	0.49 ± 0.29	0.43 ± 0.29	0.24 ± 0.19	0.77 ± 0.31	0.54 ± 0.34	0.55 ± 0.28
Chicken intake (servings · d^{-1} · 1000 kcal^{-1})	0.16 ± 0.13	0.19 ± 0.14	0.13 ± 0.10	0.22 ± 0.18	0.20 ± 0.13	0.18 ± 0.12
Fish intake (servings · d^{-1} · 1000 kcal^{-1})	0.15 ± 0.15	0.19 ± 0.17	0.16 ± 0.15	0.17 ± 0.17	0.18 ± 0.15	0.16 ± 0.13
Total energy intake (kcal/d)	1833 ± 593	1953 ± 604	1989 ± 620	1928 ± 608	1955 ± 572	2018 ± 558

[1] *P* for trend < 0.05 for all variables except polyunsaturated fat intake by quintiles of heme-iron intake and alcohol consumption and whole-grain intake by categories of lifetime number of blood donations. MET, metabolic equivalent.

[2] $\bar{x}$ ± SD.

[3] Composite score of 24 vegetables and vegetable juices.

[4] Composite score of 18 fruits and fruit juices.

[5] Sum of intakes of beef, pork, or lamb (main dish or mixed dish); hamburgers; hot dogs; bacon; and other processed meats.

intakes of total energy, *trans* fat, cereal fiber, magnesium, whole grains, and vegetables and fruit; the ratio of polyunsaturated fat intake to saturated fat intake; glycemic load; and multivitamin use (27). All *P* values were two-sided. Tests for trend were conducted by using the median value for each category of an exposure as a continuous variable. All analyses were performed with SAS version 6.12 software (SAS Institute Inc, Cary, NC).

RESULTS

During 422 846 person-years of follow-up from 1986 to 1998, we ascertained 1168 incident cases of type 2 diabetes. The men in the highest quintile of total iron intake were less likely to smoke and drink alcohol and more likely to exercise and take multivitamin supplements than were the men in the lowest quintile (**Table 1**). High total iron intakes were associated with low intakes of saturated fat, *trans* fat, and red meat; high intakes of cereal fiber, magnesium, whole grains, fruit, and vegetables; and high glycemic load. We divided total dietary iron into heme iron (found in animal products) and nonheme iron (found in plants and obtained from supplements) because absorption of heme iron is more complete and less regulated than is that of nonheme iron (28). The men in the highest quintile of heme-iron intake were more likely to smoke and less likely to exercise and take multivitamin supplements than were the men in the lowest quintile. The men in the highest quintile of heme-iron intake also tended to have lower intakes of cereal fiber, magnesium, whole grains, fruit, and vegetables; a lower glycemic load; and higher intakes of saturated fat, *trans* fat, chicken, and red meat (Table 1). Because nonheme iron accounted for most of the iron intake, and the results for nonheme-iron intake were largely similar to those for total iron intake, we did not include the data for nonheme iron in this report. The blood donors had a higher prevalence of family history of diabetes and multivitamin use than did the nondonors. The distributions of the other risk factors for type 2 diabetes among the blood donors and the nondonors were similar, although the trend tests were significant because of the large sample size.

Total iron intake was inversely associated with the risk of type 2 diabetes in the analyses adjusted for age and for age and BMI but not in the multivariate analysis with adjustment for family history of diabetes, physical activity, cigarette smoking, alcohol consumption, and dietary factors (**Table 2**). Heme-iron intake was associated with an elevated risk of type 2 diabetes. In the age-adjusted analysis, the risk for the men in the highest quintile of heme-iron intake relative to that for the men in the lowest quintile was 2.11 (95% CI: 1.74, 2.56; *P* for trend < 0.001). In multivariate models, BMI was the strongest confounder. The relative risk was attenuated to 1.47 (95% CI: 1.21, 1.79) after adding BMI to the model. After further ad-

TABLE 2
Relative risks (RRs) of type 2 diabetes according to quintiles of total iron and heme-iron intake[1]

	Quintile of intake					
	1	2	3	4	5	*P* for trend
Total iron						
Median intake (mg/d)	11.1	13.1	15.2	19.7	34.2	—
No. of cases	237	253	267	224	187	—
Age-adjusted RR	1.0	1.06 (0.88, 1.26)	1.14 (0.95, 1.36)	0.92 (0.77, 1.11)	0.78 (0.64, 0.94)	<0.001
Age- and BMI-adjusted RR	1.0	1.03 (0.86, 1.23)	1.17 (0.97, 1.39)	0.99 (0.82, 1.19)	0.87 (0.71, 1.05)	0.03
Multivariate-adjusted RR[2]	1.0	1.10 (0.91, 1.33)	1.36 (1.11, 1.66)	1.23 (0.99, 1.53)	1.16 (0.92, 1.47)	0.67
Heme iron						
Median intake (mg/d)	0.80	1.05	1.27	1.50	1.90	—
No. of cases	159	189	253	254	313	—
Age-adjusted RR	1.0	1.22 (0.99, 1.51)	1.57 (1.28, 1.92)	1.70 (1.39, 2.07)	2.11 (1.74, 2.56)	<0.001
Age- and BMI-adjusted RR	1.0	1.08 (0.87, 1.34)	1.28 (1.05, 1.57)	1.28 (1.04, 1.57)	1.47 (1.21, 1.79)	<0.001
Multivariate-adjusted RR[2]	1.0	1.09 (0.87, 1.36)	1.28 (1.03, 1.58)	1.22 (0.98, 1.53)	1.28 (1.02, 1.61)	0.045

[1] 95% CI in parentheses.
[2] Adjusted for BMI (in kg/m^2; <21, 21.0–22.9, 23.0–24.9, 25.0–27.9, 28.0–29.9, 30.0–34.9, ≥35, and missing information); family history of diabetes in a first-degree relative (yes or no); physical activity (quintiles of metabolic equivalents); cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d); alcohol consumption (0, 0.1–5.0, 5.1–15.0, 15.1–30.0, 30.1–50.0, and >50.0 g/d); intakes of total energy, *trans* fat, cereal fiber, magnesium, whole grains, vegetables, and fruit (in quintiles); ratio of polyunsaturated fat intake to saturated fat intake (in quintiles); glycemic load (in quintiles); and multivitamin use (no use and use of 0–1, 2–4, 5–9, and ≥10 y).

justment for family history of diabetes, physical activity, cigarette smoking, alcohol consumption, total energy intake, and other dietary variables, heme-iron intake remained significantly associated with the risk of type 2 diabetes (relative risk: 1.28; 95% CI: 1.02, 1.61; *P* for trend = 0.045). However, the positive association disappeared after additional adjustment for red meat intake (relative risk: 0.96; 95% CI: 0.74, 1.23; *P* for trend = 0.58).

Because red meat was a major contributor to heme-iron intake, and red meat itself is positively associated with the risk of type 2 diabetes (29), we further subdivided heme-iron intake on the basis of 2 sources (red meat and sources other than red meat) and then examined each source in relation to diabetes risk. We observed that diabetes risk increased with increasing heme-iron intakes from red meat (multivariate relative risk comparing quintile 5 with quintile 1: 1.63; 95% CI: 1.26, 2.10; *P* for trend < 0.001) but not with increasing heme-iron intake from sources other than red meat, such as chicken and fish (relative risk: 0.98; 95% CI: 0.80, 1.21; *P* for trend = 0.87) (**Figure 1**). We also conducted multivariate analyses of the relation between heme-iron intake and diabetes risk within strata defined by BMI values and alcohol intakes and found no apparent modification of the relation by these factors.

We found no appreciable association between blood donations and the risk of type 2 diabetes (**Table 3**). Relative to the men who never donated blood, the men in the highest category of blood donations (≥30) had an age-adjusted relative risk of diabetes of 1.23 (95% CI: 0.87, 1.75; *P* for trend = 0.19) and a multivariate relative risk of 1.12 (95% CI: 0.78, 1.61; *P* for trend = 0.70).

DISCUSSION

In this large prospective cohort study of men, we found that neither total iron intake nor blood donations were associated with risk of type 2 diabetes. Heme-iron intake from red meat was positively associated with the risk of type 2 diabetes. However, the association may have been confounded by other components of red meat intake because heme-iron intake from sources other than red meat (eg, fish, chicken, and egg) was not associated with the risk of type 2 diabetes.

Prospective data relating iron stores to the risk of type 2 diabetes are scarce. To our knowledge, this is the first prospective cohort study to directly examine the associations of dietary

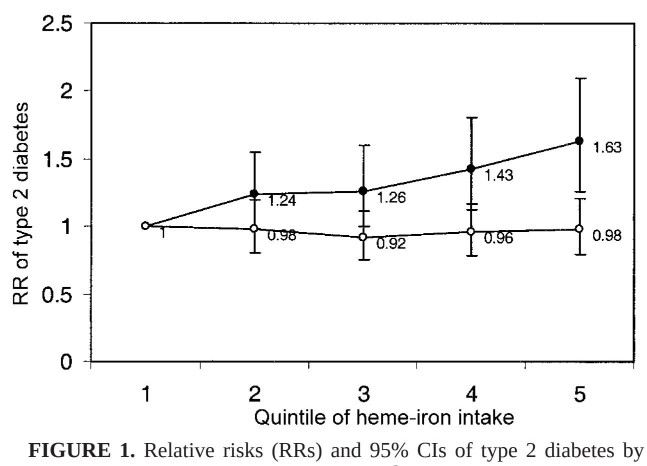

FIGURE 1. Relative risks (RRs) and 95% CIs of type 2 diabetes by quintile of heme-iron intake from red meat (●) and sources other than red meat (○). RRs were multivariate adjusted for BMI (in kg/m^2; <21, 21.0–22.9, 23.0–24.9, 25.0–27.9, 28.0–29.9, 30.0–34.9, ≥35, and missing information); family history of diabetes in a first-degree relative (yes or no); physical activity (quintiles of metabolic equivalents); cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d); alcohol consumption (0, 0.1–5.0, 5.1–15.0, 15.1–30.0, 30.1–50.0, and >50.0 g/d); intakes of total energy, *trans* fat, cereal fiber, magnesium, whole grains, vegetables, and fruit (in quintiles); the ratio of polyunsaturated fat intake to saturated fat intake (in quintiles); glycemic load (in quintiles); and multivitamin use (no use and use of 0–1, 2–4, 5–9, and ≥10 y). The median values for quintiles 1–5 of heme-iron intake from red meat were 0.20, 0.45, 0.63, 0.90, and 1.30 mg/d, respectively; the median values for quintiles of heme-iron intake from sources other than red meat were 0.21, 0.40, 0.55, 0.70, and 1.00 mg/d, respectively.

TABLE 3
Relative risks (RRs) of type 2 diabetes according to lifetime number of blood donations assessed in 1992[1]

	No. of blood donations						
	0	1–5	6–9	10–19	20–29	≥ 30	*P* for trend
No. of cases	239	193	62	60	36	38	—
Person-years	74 994	55 517	19 743	18 914	8654	9160	—
Age-adjusted RR	1.0	1.08 (0.89, 1.31)	1.00 (0.75, 1.32)	1.00 (0.75, 1.33)	1.28 (0.90, 1.82)	1.23 (0.87, 1.75)	0.19
Age- and BMI-adjusted RR	1.0	1.08 (0.89, 1.30)	0.95 (0.72, 1.27)	0.91 (0.68, 1.22)	1.13 (0.79, 1.62)	1.14 (0.80, 1.61)	0.69
Multivariate-adjusted RR[2]	1.0	1.05 (0.86, 1.28)	0.94 (0.70, 1.26)	0.91 (0.67, 1.22)	1.13 (0.78, 1.62)	1.12 (0.78, 1.61)	0.70

[1] 95% CI in parentheses.

[2] Adjusted for BMI (in kg/m^2; <21, 21.0–22.9, 23.0–24.9, 25.0–27.9, 28.0–29.9, 30.0–34.9, ≥35, and missing information); family history of diabetes in a first-degree relative (yes or no); physical activity (quintiles of metabolic equivalents); cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d; alcohol consumption (0, 0.1–5.0, 5.1–15.0, 15.1–30.0, 30.1–50.0, and >50.0 g/d); intakes of total energy, *trans* fat, cereal fiber, magnesium, whole grains, vegetables, and fruit (in quintiles); ratio of polyunsaturated fat intake to saturated fat intake (in quintiles); glycemic load (in quintiles); and multivitamin use (no use and multivitamin use of 0–1, 2–4, 5–9, and ≥10 y).

iron intake and blood donations with diabetes incidence, which is important because dietary iron intake and blood donations are factors that might be altered if excess iron stores were thought to be causally related to diabetes. Findings from cross-sectional and case-control studies relating serum ferritin concentrations to insulin resistance or risk of diabetes were inconsistent (6–11, 30, 31). Several of these studies observed positive associations between serum ferritin concentrations and insulin resistance (6–8) or risk of diabetes (10, 11). However, high serum ferritin concentrations may reflect systemic inflammation associated with diabetes rather than high body iron stores. Salonen et al (5) examined the relation between the ratio of serum transferrin receptor concentration to ferritin concentration and the incidence of diabetes in a small, nested case-control study (41 cases and 82 controls) in Finland. The men in the lowest quartile of the ratio of transferrin receptor to ferritin were 2.4 times as likely as the men in the highest quartile to develop diabetes. Because the ratio of transferrin receptor to ferritin was not associated with inflammation, this Finnish study provides some evidence that iron overload may be a risk factor for diabetes. However, Salonen et al did not assess the association of diabetes incidence with dietary iron intake and blood donations.

Dietary iron intake is an important determinant of body iron stores, especially in men and postmenopausal women who have no physiologic mechanism to eliminate excess iron (13, 28). Heme iron, which is present in red meat, fish, and poultry, is highly bioavailable and contributes about one-half of the total bioavailable iron in the typical US diet (32). A potential concern in this analysis is that imperfect assessment of diet might have led to an underestimation of the true effect. However, the repeated measurements of diet with a validated food-frequency questionnaire accounted for dietary changes and reduced measured error (33). Moreover, high heme-iron intakes have been associated with high plasma ferritin concentrations in our cohort (34).

Misclassification of blood donation was inevitable because self-reported data on blood donations were used, and the recall bias for the history of blood donations in the past 30 y may have been large. In addition, the relatively short follow-up for the analysis of blood donations and diabetes risk may have limited the power to detect an association. Nevertheless, blood donations have been associated with lower ferritin concentrations in this study population (18). The 3-fold difference in serum ferritin concentrations between the frequent donors and the nondonors indicates the validity of using self-reported data on blood donations as another determinant of body iron stores. Furthermore, the high follow-up rate (98%) minimized potential bias due to loss to follow-up. Self-reported diabetes was confirmed by a supplementary questionnaire and was validated through medical records review. Some underdiagnosis of diabetes was likely. However, some degree of underascertainment of diabetes, if not associated with exposure, would not have affected the associations (35).

We recognize that blood donors in this cohort may not be representative of the general population. Specifically, the blood donors in this cohort tend to be more health conscious and tend to have healthier diets, but we adjusted carefully for these variables. However, the biological effects of iron among blood donors in this cohort would be expected to be the same as those among blood donors in the general population, and our cohort is well characterized with respect to diet and lifestyle factors. Most importantly, blood donors have lower ferritin concentrations (reflecting lower iron stores), and this relation is dependent on the number of donations (18).

Although severe iron overload can cause type 2 diabetes among patients with hemochromatosis [up to 65% of hemochromatosis patients develop diabetes (36)], our study found no evidence that total iron intake or the frequency of blood donations is related independently to the risk of type 2 diabetes in apparently healthy middle-aged men. However, heme-iron intake from red meat appears to be associated with an increased risk of type 2 diabetes, but our study was unable to determine whether the association was due to heme iron per se or to other components of red meat. Further cohort studies are needed to examine iron intake and direct measures of body iron stores in relation to the risk of diabetes.

RJ contributed to the study design, data analysis, and the drafting of the manuscript. MJS, WCW, and FBH contributed to the study design and data collection. All the authors contributed to data interpretation and revision of the manuscript. None of the authors had any relevant personal or financial conflicts of interest.

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