

Heme Iron Intake and Risk of Stroke

A Prospective Study of Men

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Background and Purpose—Intake of iron, especially heme iron, has been associated with several diseases. However, epidemiological studies of heme iron and nonheme iron intake in relation to risk of stroke are lacking. The aim of this study was to examine the associations between heme iron and nonheme iron intake and stroke incidence in men.

Methods—The population-based prospective Cohort of Swedish Men included 38 859 men, aged 45 to 79 years, who had no history of stroke, coronary heart disease, or cancer at baseline. Hazard ratios and 95% confidence intervals (95% CIs) were calculated using Cox proportional hazards regression models.

Results—During an 11.7 years follow-up, 3097 incident cases of stroke, including 2482 cerebral infarctions and 450 intracerebral hemorrhages, were registered. The hazard ratios of total stroke and cerebral infarction for the highest compared with the lowest quintiles of heme iron intake were 1.16 (95% CI, 1.03–1.31; P trend=0.037) and 1.15 (95% CI, 1.00–1.31; P trend=0.089), respectively. The incidence rates of total stroke per 10 000 person-years were 72.6 in the lowest quintile and 84.4 in the highest. The association was confined to men with body mass index <25 kg/m², the hazard ratios were 1.40 (95% CI, 1.17–1.68; P trend<0.001) for total stroke and 1.38 (95% CI, 1.13–1.70; P trend=0.001) for cerebral infarction; no association was observed among overweight and obese men. There was no association between nonheme iron intake and risk of total stroke and stroke types.

Conclusions—Findings from this prospective study indicate that a high heme iron intake, particularly in normal weight individuals, may increase the risk of stroke. (*Stroke*. 2013;44:334-339.)

Key Words: heme iron ■ incidence ■ nonheme iron ■ prospective studies ■ stroke

Recently published studies indicate that consumption of red meat may be related to risk of developing stroke.^{1–3} This association has been ascribed, at least partly, to heme iron, which is present in red meat. Heme iron can promote oxidative stress, leading to subsequent cell apoptosis and cell death.^{4,5} High doses of iron may lead to increased peroxidation of lipids,^{6–8} protein modification, and DNA damage.^{8,9} Elevated iron stores caused by a high iron intake have been positively associated with inflammation,¹⁰ insulin resistance,¹¹ the metabolic syndrome,¹² and the risk of coronary heart disease,^{13,14} type 2 diabetes mellitus,¹⁵ and some types of cancers.^{16–20}

To our knowledge, no study has examined heme iron and nonheme iron separately in relation to stroke risk. Only a few studies have investigated the relation between total iron intake and risk of stroke, and the results are inconsistent.^{21–23}

Identification of nutritional factors that affect the risk of stroke is relevant from a public health point of view. According to the American Heart Association Report, each year about 795 000 individuals experience a new or recurrent

stroke, and every 4 minutes in USA someone dies from the disease.²⁴

Therefore, we conducted a prospective study to investigate the association of heme iron and nonheme iron intake with risk of total stroke and stroke types. We analyzed data from 38 859 participants in the population-based Cohort of Swedish Men followed up during 11.7 years.

Methods

Study Population

The Cohort of Swedish Men was established in central Sweden (Västmanland and Örebro Counties) in 1997–1998. A questionnaire was sent to all men in the age group from 45 to 79 years living in this area. A total of 48 850 men (49%) returned a completed questionnaire. For the present analysis, we excluded men with an incomplete questionnaire and those with an erroneous or missing national identification number or implausible values for total energy intake (ie, 3 SDs from the mean value for log-transformed energy). Moreover, we further excluded men with a history of stroke, coronary heart disease, or cancer (other than nonmelanoma skin cancer) at baseline. After

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these exclusions, this study included 38 859 men. The study was approved by the Regional Ethical Committee at Karolinska Institutet (Stockholm, Sweden).

Assessment of Diet and Other Exposure

Usual frequency of food consumption over the past year was estimated from a 96-item food frequency questionnaire of commonly consumed foods in Sweden as well as foods with high concentration of some nutrients and bioactive substances. Participants were asked to indicate how often they had consumed various foods/food items. Frequency of consumption was reported according to 8 possible categories: never/seldom, 1 to 3 times per month, 1 to 2 times per week, 3 to 4 times per week, 5 to 6 times per week, once a day, 2 times a day, and ≥ 3 times per day. Intakes of total iron and other nutrients were calculated by multiplying the frequency of consumption of each food item by the nutrient content (obtained from the Swedish Food Administration Database)²⁵ of appropriate age-specific portion sizes.

The heme iron content in all meat and fish items was calculated using a method developed by Balder et al.²⁶ The average of the measured values of heme iron content of specific types of meat reported in the published literature²⁶ was used to generate the heme iron specific factor for a given food item, ranging from 0.01 for shellfish to 0.70 for blood pudding. For each meat and fish item, the type-specific heme iron factor was multiplied with its total iron content to derive the heme iron content of that item. Nonheme iron was calculated as total iron intake minus heme iron.

The food frequency questionnaire has been validated for nutrients among 248 men aged 40 to 74 years. The mean Spearman correlation coefficients between estimates from the food frequency questionnaire and the mean of 14 24-hour recall interviews were 0.65 for macronutrients and 0.62 for micronutrients.²⁷

Data about education, smoking status, body height and weight, physical activity, history of hypertension and high blood cholesterol level, aspirin use, family history of myocardial infarction before 60 years of age, and alcohol drinking habits were collected by using a self-administered questionnaire completed at baseline. Participants reported their level of activity at home/housework, work, walking/bicycling, and leisure-time exercise in the year before study enrollment. In the questionnaire were also questions regarding inactivity (watching television and reading) and hours per day of sleeping and sitting/lying down. The time spend per day at each activity was multiplied by its energy expenditure requirements (expressed in metabolic equivalents and added together to create a total physical activity score.²⁸ The body mass index (BMI) was calculated by dividing participants' weight (in kilograms) by the square of their height (in meters).

Participants were classified as having diabetes mellitus if they self-reported it on the questionnaire or had a diagnosis of the disease recorded in the Swedish National Inpatient Register or the Swedish National Diabetes Register.

Case Ascertainment and Follow-up

Incident cases of first stroke that occurred between January 1, 1998 and December 31, 2010 were ascertained by linkage of the study cohort with the Swedish Hospital Discharge Registry, which completeness is nearly 100%. The International Classification of Diseases 10th revision was used to identify stroke events. Strokes were classified as cerebral infarction (International Classification of Diseases-10 code I63), intracerebral hemorrhage (I61), subarachnoid hemorrhage (I60), and unspecified stroke (I64). Dates of death were obtained from the Swedish Death Registry.

Statistical Analysis

Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals (95% CIs) of total stroke and stroke types (cerebral infarction and intracerebral hemorrhage). We categorized participants into quintiles of heme and nonheme iron intake.

Multivariable hazard ratio estimates were adjusted for age (continuous variable), education (less than high school, high school, or

university), smoking status and pack-years of smoking (never; past <20, 20–39, or ≥ 40 pack-years; or current <20, 20–39, or ≥ 40 pack-years), BMI (<20, 20–24.9, 25–29.9, or ≥ 30 kg/m²), total physical activity score (quartiles), history of hypertension (yes or no), history of high blood cholesterol (yes or no), diabetes mellitus (yes or no), aspirin use (yes or no), family history of myocardial infarction before 60 years of age (yes or no), alcohol consumption (quintiles), and quintiles of intake of dietary fiber, vitamin E, β -carotene, vitamin C, and calcium. All nutrients were energy-adjusted using the residual method.²⁹ Multivariable hazard ratios were mutually adjusted for heme iron and nonheme iron intake. All covariates were prespecified and included to the models because they are known risk factors of stroke (nondietary covariates) or potential dietary confounders related to both stroke and heme or nonheme iron intake, metabolism, and absorption. For example, vitamin C affects absorption of iron (especially nonheme iron) by reducing ferric iron to the more soluble and absorbable ferrous form,³⁰ whereas high calcium intake can decrease iron absorption.³¹ Furthermore, as antioxidants, vitamin C, vitamin E, and β -carotene may protect against damage from free radicals induced by iron.⁴

The proportional hazards assumption was evaluated by regressing scaled Schoenfeld residuals against survival time. There was no evidence of departure from the assumption. Tests for linear trend were conducted by using values of heme iron and nonheme iron intake as continuous variables. In exploratory analyses, we examined whether the association of heme iron and nonheme iron intake with stroke risk was modified by major risk factors for stroke, including BMI (<25 kg/m²; ≥ 25 kg/m²), smoking status (current; never or past), physical activity (score: <40.9 metabolic equivalent \times hour/d [median]; \geq median), and alcohol consumption (ethanol consumption: <15.4 g/d [median]; \geq median). Test for interaction was conducted using the likelihood ratio test. The statistical analyses were performed by using SAS version 9.2 (SAS Institute Inc. Cary, NC). All reported *P* values were 2-sided, and *P* ≤ 0.05 were considered statistically significant.

Results

Age-standardized characteristics of study population by quintiles of energy-adjusted heme iron and nonheme iron intake are shown in Table I and Table II, respectively, in the online-only Data Supplement. The Spearman correlation between heme iron and nonheme iron intake was 0.18 (*P*<0.001). Median intakes of heme iron and nonheme iron differed 2.6-fold and 1.8-fold, respectively, between the lowest and the highest quintiles. Men in the highest quintile of heme iron intake consumed 2.6-times more red meat than those in the lowest quintile (149 \pm 79 versus 58 \pm 29 g/d), whereas men in the highest quintile of nonheme iron intake consumed 1.2-times more red meat compared with men in the lowest quintile (114 \pm 69 versus 94 \pm 51 g/d). Compared with men in the lowest quintile of heme iron intake, those in the highest quintile were younger and were more likely to have a history of hypertension. More men in the lowest quintile of nonheme iron intake were current smokers than men in the highest quintile. Men with a high intake of heme iron and nonheme iron were more likely to have a university education and to have diabetes compared with those with a low intake. Moreover, men with high intakes of heme and nonheme iron had, on average, higher intakes of β -carotene, vitamin C, and dietary fiber but a lower intake of calcium than men with a low iron intake.

During a mean of 11.7 years of follow-up (454 792 person-years, 1998–2010), we ascertained 3097 incident cases of stroke, including 2482 cerebral infarctions and 450 intracerebral hemorrhages.

We observed a positive association between heme iron intake and risk of total stroke and cerebral infarction, but not

intracerebral hemorrhage (Table 1). Compared with men in the lowest quintile of heme iron intake, those in the highest quintile had a 16% (95% CI, 3%–31%) and 15% (95% CI, 0%–31%) higher risk of total stroke and cerebral infarction, respectively. The age-standardized incidence rates of total stroke per 10 000 person-years were 72.6 in men with the lowest quintile of heme intake and 84.4 in those with the highest quintile. There was no association between nonheme iron intake and risk of total stroke or any stroke type.

Adjustment for total red meat consumption (in quintiles), which was highly correlated with heme iron intake ($r=0.64$), did not change the results materially; the hazard ratios for the highest category of heme iron intake compared with the lowest category were 1.16 (95% CI, 1.01–1.34) for total stroke and 1.17 (95% CI, 1.00–1.37) for cerebral infarction. Given the high correlation between heme iron and red meat consumption, the results adjusted for red meat are merely hypothesis generating and should be interpreted cautiously. Adding

quintiles of saturated fatty acid intake (correlation with heme iron intake, $r=-0.11$), instead of red meat consumption to the multivariable model, did not appreciably change the results for total stroke (hazard ratio=1.16; 95% CI, 1.02–1.31) or cerebral infarction (hazard ratio=1.14; 95% CI, 0.99–1.31).

Exclusion of the first 1 year of follow-up did not substantially change the observed risk estimates. Men in the highest, compared with the lowest, quintile of heme iron intake had a 17% higher risk of total stroke (95% CI, 3%–32%) and a 15% higher risk of cerebral infarction (95% CI, 0%–33%).

Furthermore, we examined whether the association between heme iron and nonheme iron intake and total stroke and types of stroke incidence varied by categories of BMI, smoking status, physical activity, and alcohol consumption. We observed a statistically significant interaction between heme iron intake and BMI in relation to total stroke (P for interaction=0.03) and a tendency in relation to cerebral infarction (P for interaction=0.095; Table 2). Among men with

Table 1. Hazard Ratios (95% Confidence Intervals) of Total Stroke and Stroke Types by Quintiles of Heme Iron and Nonheme Iron Intake in 38 859 Swedish Men, 1998–2010

	Heme Iron Intake (mg/d) (Median)					<i>P</i> for trend
	<1.28 (1.04)	1.28–1.61 (1.46)	1.62–1.92 (1.76)	1.93–2.33 (2.10)	≥2.34 (2.69)	
Total stroke						
Person-years	88 272	90 535	92 104	92 514	91 368	
No. of cases	751	651	567	532	596	
Age adjusted	1.00	1.02 (0.92–1.14)	1.00 (0.90–1.12)	1.02 (0.91–1.14)	1.18 (1.06–1.31)	0.005
Multivariable model*	1.00	1.07 (0.96–1.19)	1.04 (0.93–1.17)	1.04 (0.93–1.18)	1.16 (1.03–1.31)	0.037
Cerebral infarction						
No. of cases	605	520	469	419	469	
Age adjusted	1.00	1.02 (0.91–1.15)	1.04 (0.92–1.17)	1.00 (0.89–1.14)	1.16 (1.03–1.31)	0.023
Multivariable model*	1.00	1.07 (0.95–1.20)	1.09 (0.96–1.23)	1.03 (0.90–1.18)	1.15 (1.00–1.31)	0.089
Intracerebral hemorrhage						
No. of cases	104	104	80	79	83	
Age adjusted	1.00	1.15 (0.88–1.51)	0.98 (0.73–1.31)	1.03 (0.77–1.39)	1.11 (0.83–1.49)	0.632
Multivariable model*	1.00	1.17 (0.88–1.54)	0.98 (0.72–1.33)	1.03 (0.75–1.41)	1.06 (0.76–1.46)	0.834
	Nonheme Iron Intake (mg/d) (Median)					<i>P</i> for trend
	<10.6 (9.4)	10.6–12.2 (11.5)	12.3–13.6 (13.0)	13.7–15.4 (14.5)	≥15.5 (16.9)	
Total stroke						
Person-years	88 325	90 998	91 442	92 193	91 834	
No. of cases	713	636	553	602	593	
Age adjusted	1.00	0.89 (0.80–0.99)	0.80 (0.71–0.89)	0.90 (0.80–1.00)	0.91 (0.82–1.02)	0.156
Multivariable model*	1.00	0.95 (0.85–1.07)	0.88 (0.78–1.01)	0.99 (0.87–1.15)	0.99 (0.85–1.14)	0.627
Cerebral infarction						
No. of cases	569	498	453	491	471	
Age adjusted	1.00	0.88 (0.78–0.99)	0.82 (0.72–0.93)	0.92 (0.81–1.04)	0.91 (0.80–1.03)	0.196
Multivariable model*	1.00	0.92 (0.81–1.05)	0.89 (0.77–1.03)	0.99 (0.85–1.16)	0.95 (0.81–1.12)	0.959
Intracerebral hemorrhage						
No. of cases	101	107	71	80	91	
Age adjusted	1.00	1.06 (0.81–1.39)	0.72 (0.53–0.97)	0.83 (0.62–1.11)	0.97 (0.73–1.29)	0.441
Multivariable model*	1.00	1.24 (0.92–1.67)	0.91 (0.64–1.30)	1.09 (0.75–1.57)	1.29 (0.88–1.90)	0.413

*Adjusted for age, education, smoking status and pack-years of smoking, body mass index, total physical activity, history of hypertension, high blood cholesterol level, diabetes mellitus, aspirin use, family history of myocardial infarction, alcohol intake and intake of dietary fiber, vitamin E, β -carotene, vitamin C, and calcium. Heme and nonheme iron were mutually adjusted.

Table 2. Hazard Ratios (95% Confidence Intervals) of Total Stroke and Cerebral Infarction by Quintiles of Heme Iron Intake Stratified by Body Mass Index

	Heme Iron Intake (mg/d) (Median)					P for trend
	<1.28 (1.04)	1.28–1.61 (1.46)	1.62–1.92 (1.76)	1.93–2.33 (2.10)	≥2.34 (2.69)	
Body mass index <25 kg/m ²						
Total stroke						
No. of persons	3881	3812	3753	3632	3437	
Person-years	44 040	44 474	44 368	43 133	40 151	
No. of cases	341	284	253	219	266	
Age adjusted	1.00	1.02 (0.87–1.20)	1.05 (0.89–1.24)	1.04 (0.87–1.23)	1.39 (1.18–1.63)	<0.001
Multivariable model*	1.00	1.09 (0.93–1.28)	1.14 (0.96–1.35)	1.10 (0.92–1.32)	1.40 (1.17–1.68)	<0.001
Cerebral Infarction						
No. of cases	276	226	212	162	210	
Age adjusted	1.00	1.00 (0.84–1.20)	1.10 (0.91–1.31)	0.95 (0.78–1.16)	1.35 (1.13–1.62)	<0.001
Multivariable model*	1.00	1.07 (0.90–1.28)	1.20 (0.99–1.44)	1.02 (0.83–1.26)	1.38 (1.13–1.70)	0.001
Body mass index ≥25 kg/m ²						
Total stroke						
No. of persons	3889	3960	4019	4139	4337	
Person-years	44 231	46 062	47 736	49 381	51 216	
No. of cases	410	367	314	313	330	
Age adjusted	1.00	1.02 (0.88–1.17)	0.96 (0.82–1.11)	0.98 (0.85–1.14)	1.02 (0.88–1.18)	0.823
Multivariable model*	1.00	1.04 (0.90–1.20)	0.97 (0.83–1.14)	1.00 (0.85–1.17)	1.00 (0.85–1.18)	0.614
Cerebral Infarction						
No. of cases	329	294	257	257	259	
Age adjusted	1.00	1.03 (0.88–1.20)	0.99 (0.84–1.17)	1.02 (0.87–1.21)	1.01 (0.86–1.19)	0.665
Multivariable model*	1.00	1.04 (0.88–1.22)	1.01 (0.85–1.20)	1.04 (0.87–1.24)	0.99 (0.83–1.19)	0.536

*Adjusted for age, education, smoking status and pack-years of smoking, total physical activity, history of hypertension, high blood cholesterol level, diabetes mellitus, aspirin use, family history of myocardial infarction, alcohol intake and intake of dietary fiber, vitamin E, β -carotene, vitamin C, and calcium. Heme and nonheme iron were mutually adjusted.

normal weight (BMI <25 kg/m²), those in the highest quintile of heme iron intake compared with those in the lowest quintile had a 40% (95% CI, 17%–68%) higher risk of total stroke and a 38% (95% CI, 13%–70%) higher risk of cerebral infarction. There was no relation between heme iron intake and total stroke and cerebral infarction among overweight and obese men (BMI ≥25 kg/m²). There were no interactions observed between heme iron intake and smoking status, physical activity, or alcohol consumption (all *P* for interaction >0.1).

Discussion

In this population-based, prospective study of men, intake of heme iron, but not nonheme iron, was associated with an increased risk of total stroke and cerebral infarction. Men in the highest, compared with the lowest, quintile of heme iron intake had a statistically significant 16% and 15% higher incidence of total stroke and cerebral infarction, respectively. The difference in consumption of red meat between men in the corresponding quintiles was 91 g/d. The increased risk of stroke associated with heme iron intake was only observed among men in the highest quintile of heme iron. Lower heme iron intake was not significantly associated with stroke risk. Moreover, the observed association was confined to normal weight men among whom the risk of developing stroke was 40% higher for those in the highest quintile of heme iron.

There are no previously published studies on heme and nonheme iron intake in relation to stroke incidence or stroke mortality. A few epidemiological studies have investigated the relation between total iron intake and incidence of stroke with conflicting results.^{21–23} In a case-control study, high intake of total iron was related to a nonsignificant increased risk of ischemic stroke.²¹ In one prospective study, there was a statistically significant inverse association between total iron intake and risk of ischemic stroke,²³ but not in other.²² There are also a few prospective studies^{32–34} and studies of stroke patients^{35–37} relating iron status in blood to risk of stroke. Most of those studies,^{32,33,35–37} but not all,³⁴ indicate a positive association between serum ferritin levels and risk of stroke.

Heme iron is characterized by a much higher bioavailability than nonheme iron. The main source of heme iron is meat, especially red meat, offal (liver, kidney) and blood pudding, where heme iron is a part of hemoglobin and myoglobin. Nonheme iron encompasses many diverse forms of iron and is present in both plant and animal foods. Although heme is absorbed intact, the bioavailability of nonheme iron depends on many different complexes and factors that can either improve (eg, vitamin C) or impair (eg, phytates, tannins) the absorption.³⁰ Based on the absorption measurements, it was determined that heme iron absorption (37% of total heme iron intake with diet) was much greater than nonheme iron

absorption (5% of total nonheme iron intake).³⁸ Because of the large differences in absorption of the 2 forms of iron, human iron status is mainly dependent on heme iron intake.

The potential adverse effect of heme iron may be attributed to its pro-oxidative properties. It catalyzes the conversion of superoxide and hydrogen peroxide into hydroxyl radicals in the Fenton reaction.⁴ There is evidence that increased iron accumulation in endothelial cell in the brain can contribute to stroke progression and worse prognosis among patients.^{5,39} Results from animal studies indicate that the use of a chelating agent to remove excess iron after incidence of some types of stroke gives valuable results, such as reduction of intraventricular hemorrhage,⁴⁰ reduction of oxidative stress, and neuronal cell death.⁴¹ Moreover, other components found in animal products, specifically in processed meat, which are highly correlated with heme iron intake, such as *N*-nitroso compounds⁴² and heterocyclic amines, can contribute to the occurrence of stroke. However, our results did not change essentially when we adjusted for red meat consumption, suggesting that the observed association between heme iron and stroke is not confounded by other factors in red meat in this study population.

In the present study, a significant association between heme iron intake and stroke was observed only in normal weight men. The lack of association in overweight and obese men may be attributed to the chronic inflammatory condition associated with obesity.⁴³ Increased expression of proinflammatory cytokines, such as interleukin-6 or tumor necrosis factor- α , can result in the expression and release of hepcidin, a hormone produced by the liver that can act as an inhibitor of iron absorption.^{44,45} Hepcidin can reduce iron status by direct action at the site of iron absorption as well as through the sequestration of iron at the macrophage.^{45,46} Among patients with severe obesity, a statistically significant positive correlation between adipocyte hepcidin expression and BMI was observed ($r=0.7$, $P<0.001$).⁴⁷

Strengths of this study include the population-based and prospective design, detailed information on diet, and the almost complete follow-up of study participants by linkage with various population-based Swedish registries. Additionally, this study included a large number of stroke cases, which led to high statistical power in the analysis. The extensive data on possible risk factors for stroke allowed comprehensive adjustment for confounders. Although the food frequency questionnaire-based estimates of macronutrients and micronutrients intake had relatively high validity, some misclassification of heme iron and nonheme iron intake is inevitable. Measurement error in assessing dietary intake in a prospective setting leading to nondifferential misclassification would have likely attenuated rather than exaggerated the true associations. Furthermore, we do not know whether participants' diet during the baseline year reflected their diet during the biological relevant period. Another limitation of this study is the inability to generalize the results to women and to other groups with different diet and different nutritional status, especially iron status.

In conclusion, findings from this prospective cohort study indicate that a high intake of heme iron particular in normal weight men, but not nonheme iron, may be associated with increased risk of stroke. This finding warrants confirmation in further prospective studies.

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Disclosures

None.

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ONLINE SUPPLEMENT

Table S1. Age-Standardized Characteristics of The Cohort of 38 859 Swedish Men Aged 45-79 by Quintiles of Heme Iron Intake

Characteristics†	Quintile of Heme Iron Intake (mg/d)*				
	< 1.28 (1.04)‡	1.28 – 1.61 (1.46)	1.62 – 1.92 (1.76)	1.93 – 2.33 (1.10)	≥ 2.34 (2.69)
Age (years)	62.2	60.0	58.6	57.9	57.9
University education, > 12 years (%)	15.1	16.3	17.4	18.7	19.2
Current smoker (%)	25.9	23.3	23.4	24.5	26.4
BMI (kg/m ²)	25.7	25.6	25.6	25.7	26.0
Total physical activity (MET×h/d)	42.4	42.0	41.5	41.2	41.0
History of hypertension (%)	18.3	18.8	19.7	19.7	22.2
History of high blood cholesterol level (%)	9.5	9.8	9.9	11.7	12.4
Diabetes (%)	4.2	4.5	4.2	5.1	7.6
Aspirin use (%)	29.0	29.9	30.3	30.6	30.2
Family history of myocardial infarction (%)	10.5	11.2	10.9	11.8	11.6
Alcohol, (g/d)	9.1	10.3	10.7	11.1	10.9
Energy (kcal/d)	2795	2822	2699	2561	2410
<i>Daily dietary intake*</i>					
Fibre (g)	31.3	30.6	30.4	30.1	29.3
Tocopherol (α-TE)	8.3	8.6	8.9	9.0	9.4

β -carotene (mg)	2.37	2.57	2.75	2.97	3.21
Vitamin C (mg)	97	103	109	113	117
Calcium (mg)	1644	1519	1462	1399	1295

*Energy-adjusted to 10.9 MJ/d (2 600 kcal/d) by using the residual method.¹

†Values are means if not otherwise indicated.

‡Median values in parenthesis.

Reference

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Table S2. Age-Standardized Characteristics of The Cohort of 38 859 Swedish Men Aged 45-79 by Quintiles of Non-Heme Iron Intake

Characteristics†	Quintile of Non-Heme Iron Intake (mg/d)*				
	< 10.6 (9.4)‡	10.6 – 12.2 (11.5)	12.3 – 13.6 (13.0)	13.7 – 15.4 (14.5)	≥ 15.5 (16.9)
Age (years)	60.0	59.5	59.4	58.9	58.8
University education, > 12 years (%)	12.4	15.3	18.8	20.0	20.5
Current smoker (%)	32.6	26.2	23.0	21.1	20.0
BMI (kg/m ²)	25.9	25.7	25.6	25.7	25.6
Total physical activity (MET×h/d)	41.7	41.6	41.5	41.6	41.8
History of hypertension (%)	19.2	19.3	19.6	19.7	20.8
History of high blood cholesterol level (%)	9.1	10.2	10.7	11.6	11.8
Diabetes (%)	3.3	4.1	4.6	5.4	8.3
Aspirin use (%)	29.8	31.1	29.9	30.4	29.1
Family history of myocardial infarction (%)	10.9	10.8	11.2	11.6	11.8
Alcohol, (g/d)	10.7	10.9	10.7	10.4	9.4
Energy (kcal/d)	2648	2700	2675	2635	2590
<i>Daily dietary intake*</i>					
Fibre (g)	22.2	27.4	30.5	33.6	38.0
Tocopherol (α-TE)	8.0	8.6	8.9	9.2	9.5
β-carotene (mg)	1.95	2.47	2.80	3.01	3.59

Vitamin C (mg)	88	102	109	116	126
Calcium (mg)	1616	1498	1459	1411	1335

*Energy-adjusted to 10.9 MJ/d (2 600 kcal/d) by using the residual method.¹

†Values are means if not otherwise indicated.

‡Median values in parenthesis.

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Heme Iron Intake and Risk of Stroke: A Prospective Study of Men

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