Public Health Nutrition: 9(4), 480–484 DOI: 10.1079/PHN2005869

Dietary iron intake and risk of non-fatal acute myocardial infarction

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Submitted 5 July 2005: Accepted 23 August 2005

Abstract

Objective: The relation between several measures of body iron and atherosclerotic disease, particularly acute myocardial infarction (AMI), is debated. This is of specific interest since iron is frequently included in supplementation and fortification of foods. We assessed the relation between dietary iron intake and the risk of non-fatal AMI.

Design: Case–control study. The information was collected by interviewers using a food-frequency questionnaire tested for validity and reproducibility. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were obtained by multiple unconditional logistic regression models, including terms for energy and alcohol intakea, as well as for sociodemographic factors, tobacco and other major recognised risk factors for AMI.

Setting: Milan, Italy, between 1995 and 1999.

Subjects: Cases were 507 patients, below age 79 years, with a first episode of non-fatal AMI, and controls were 478 patients admitted to hospital for a wide spectrum of acute conditions unrelated to known or potential AMI risk factors.

Results: Compared with patients in the lowest tertile of total iron intake, the OR was 0.48 (95% CI 0.29–0.82) for those in the highest tertile. The corresponding value for haem iron was 0.71 (95% CI 0.48–1.06), for non-haem, non-alcohol iron was 0.80 (95% CI 0.51–1.24) and for iron derived from alcoholic beverages was 0.60 (95% CI 0.40–0.90). Sex-specific OR for total iron intake were not heterogeneous.

Conclusions: In this Italian population dietary iron intake was inversely related to AMI risk. This inverse association may depend on other nutrients present in the major sources of iron in the Italian diet.

Keywords
Acute myocardial infarction
Case–control studies
Dietary iron
Risk factors

The hypothesis that iron may increase the risk of coronary heart disease originated from a Finnish prospective study[1] showing a twofold increase in acute myocardial infarction (AMI) among 51 men with serum ferritin levels above 200 $\mu g\,l^{-1}$. However, later studies yielded conflicting results. A meta-analysis of 12 prospective studies published before 1999, and based on a total of 7800 cases of coronary heart disease, found no association with several measures of iron status, including transferrin saturation, iron-binding capacity, serum iron and dietary iron intake[2]. The Rotterdam Study based on 124 cases found no association of AMI risk with total dietary iron, but a direct association with haem iron[3]. The 4-year follow-up of the National Health and Nutrition Examination Study (NHANES II), based on more than 1600 cases, found no association of serum ferritin level with mortality for coronary heart disease, AMI, cardiovascular disease and all-cause mortality[4]. A case–control study nested in the Kuopio Ischemic Heart Disease Risk Factor Study cohort[5] found a direct association of iron stores with AMI risk, while another study nested in the Helsinki Heart Study cohort[6] found no association of serum ferritin with AMI or cardiac death. A case–control study conducted in Greece found a direct association of dietary iron with coronary heart disease[7], and another case–control study conducted in The Netherlands found a direct association of coronary heart disease with dietary intake of haem iron, but not with total and non-haem iron[8].

Although most studies found no association, the relation between several measures of body iron and atherosclerotic disease is still debated, since iron is frequently included in supplementation and fortification of foods. We evaluated the role of dietary iron intake on non-fatal AMI in a case–control study in Italy, where the main sources of iron intake are different from those in North America and Northern Europe, and where AMI incidence is low and AMI dietary correlates are favourable[9].

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Subjects and methods

The data derive from a case–control study of non-fatal AMI, conducted between 1995 and 1999 in the greater Milan area, Italy. Cases were 507 patients (378 men, 129 women; median age 61 years, range 25–79 years) with a first episode of non-fatal AMI, defined according to the World Health Organization criteria[10], admitted to a network of teaching and general hospitals in the area. Controls were 478 patients (297 men, 181 women; median age 59 years, range 25–79 years) from the same geographical area, admitted to the same hospitals for a wide spectrum of acute conditions unrelated to known or potential AMI risk factors. Patients were not included among controls if they had been admitted to hospital for neoplastic-, metabolic- and recognised smoking- or alcohol-related conditions. Among controls, 34% had traumas, 30% non-traumatic orthopaedic disorders, 14% acute surgical conditions and 22% miscellaneous other illnesses, including ear, eye, nose, throat, skin and dental disorders. Cases and controls were excluded if they had a previous episode of AMI. Less than 5% of cases and controls approached refused interview.

Interviews were conducted in hospital using a structured questionnaire, including information on socio-demographic factors, anthropometric variables, smoking, alcohol and coffee consumption and other lifestyle habits, selected medical history, physical activity and history of AMI in relatives.

Information on diet referred to the previous 2 years and was based on a validated food-frequency questionnaire (FFQ) that included 78 foods or food groups[11,12]. Intakes of total iron, haem iron, non-haem non-alcohol iron, iron derived from alcoholic beverages and total energy were computed using an Italian food composition database[13]. The major sources of iron in the Italian diet were wine (6.5%), green salad (5.2%), vegetable soup (5.0%), red meat (4.4%), bread (4.4%), roasted or fried or stewed poultry (4.1%), apples and pears (3.9%), boiled poultry (3.4%), fish (3.2%), and crackers, grissini and melba toast (3.0%), as previously computed from this FFQ[14]. For dietary iron intake the correlation coefficient (r) was 0.66 for reproducibility, computed by comparison of the same FFQ administered twice to the same subjects in two different seasons[11], and it was 0.56 for validity, computed by comparing the FFQ with two dietary records completed in two different seasons[12].

Data analysis

Odds ratios (OR) of AMI, and the corresponding 95% confidence intervals (CI), for subsequent tertiles of iron intake were derived using unconditional multiple logistic regression models[15], including terms for age (<50, 50–59, 60–59 or ≥ 70 years), sex, education (<7, 7–10 or >10 years), body mass index (BMI) (<24, 24–27 or $>27\,kg\,m^{-2}$), blood cholesterol levels (<200, 200–237, >237 mg/100 ml, or unknown), smoking habit (never, ex-smokers, current smoker of <15 or ≥ 15 cigarettes per day), coffee (<10, 10–20 or >20 cups per week), non-alcohol energy intake (tertiles), occupational physical activity at 30–39 years (four levels), history of hyperlipidaemia (no/yes), diabetes (no/yes) and hypertension (no/yes), and family history of AMI in first-degree relatives (no/yes). Further adjustment for alcohol, vegetable and meat intake was made as appropriate, as indicated in Table 2. For example, ORs for iron intake not derived from alcoholic beverages were also adjusted for alcohol drinking. Tests for trend were based on the likelihood-ratio test between the models with and without a linear term for each variable of interest.

Results

Table 1 gives the distribution of cases and controls according to age, sex and other selected covariates. Cases were more frequently smokers and coffee drinkers; they had higher BMI and serum cholesterol levels; they consumed more pasta or rice and bread and less raw vegetables; they reported more frequently a history of hyperlipidaemia, hypertension and obesity, and AMI in first-degree relatives. No significant association was observed with various measures of cereal, meat and vegetable consumption.

The multivariate OR was 0.48 (95% CI 0.29–0.82) for patients in the highest tertile of dietary iron intake, compared with those in the lowest tertile (Table 2). Compared with patients in the lowest tertile of intake, those in the highest one had an OR of AMI of 0.71 for haem iron, 0.80 for non-haem, non-alcohol iron and 0.60 for iron derived from alcoholic beverages (mainly wine). After further adjustment for alcohol intake, the OR for total iron for the second and third tertiles compared with the first one were respectively 0.94 (95% CI 0.62–1.42) and 0.52 (95% CI 0.30–0.91) (χ^2 trend $= 4.77$, $P = 0.029$). When stratified analysis was made, using tertile cut-points computed separately for men and women, the OR was 0.58 (95% CI 0.31–1.07) in men and 0.38 (95% CI 0.14–0.98) in women for the highest level of total iron intake; these OR were not heterogeneous. The OR for the highest level of intake compared with the lowest in men was 0.59 (95% CI 0.37–0.95) for haem iron, 0.65 (95% CI 0.38–1.12) for non-haem, non-alcohol iron and 0.78 (95% CI 0.50–1.23) for iron derived from alcoholic beverages. Given the low number of women, no meaningful analyses were possible for separate sources of dietary iron in women only. The OR were not heterogeneous also in non-smokers (never and ex-smokers) (OR 0.55, 95% CI 0.28–1.06) and in current smokers (OR 0.38, 95% CI 0.15–0.94).

Discussion

Our results indicate that total iron intake does not increase the risk of non-fatal AMI, and therefore are in agreement

https://doi.org/10.1079/PHN2005869 Published online by Cambridge University Press

Table 1 Distribution of 507 cases of acute myocardial infarction (AMI) and 478 controls according to selected variables, Milan, Italy, 1995–1999

	AMI		Controls	
	n	%	*n*	%
Age (years)				
< 50	95	19	106	22
50–59	136	27	134	28
60–69	190	37	159	33
≥ 70	86	17	79	17
Sex				
Men	378	75	297	62
Women	129	25	181	38
Education (years)*				
< 7	234	46	236	49
7–10	162	32	148	31
> 10	104	21	86	18
Smoking habit				
Never smoker	151	30	198	41
Ex-smoker	125	25	134	28
Current smoker	231	46	146	31
Alcohol (drinks per week)				
Non-drinker	104	21	85	18
≤ 7	137	27	142	30
> 7–21	137	27	132	28
> 21	129	25	119	25
Coffee (cups per week)				
< 10	127	25	155	32
10–20	140	28	141	30
> 20	240	47	182	38
Body mass index (kg m^{-2})*				
< 24	125	25	146	31
24–27	178	35	148	31
> 27	202	40	176	37
Physical activity*				
1 (lowest)	83	16	50	11
2	119	24	116	25
3	158	31	173	37
4 (highest)	146	29	134	28
Cholesterol (mg/100 ml)				
< 200	51	10	55	12
≥ 200	257	51	212	44
Unknown	199	39	211	44
History of hyperlipidaemia				
No	342	67	335	70
Yes	165	33	143	30
History of hypertension				
No	348	69	359	75
Yes	159	31	119	25
Family history of AMI in first-degree relatives				
No	321	64	377	79
Yes	186	36	101	21
Diabetes				
No	433	85	448	94
Yes	74	15	30	6
Non-alcohol energy intake (kcal day^{-1})				
< 2063	164	31	160	33
2063–2628	145	29	159	33
> 2628	198	39	159	33
Bread (portions per week)				
< 14	173	34	186	39
14–20	172	34	153	32
> 20	162	32	139	29
Pasta or rice (portions per week)				
< 5	164	32	190	40
6–7	189	37	180	38
> 7	154	30	108	23
Meat (portions per week)				
< 3	216	43	188	39
4–5	145	29	140	29
> 5	146	29	150	31
Raw vegetables (portions per week)				
< 3	174	34	134	28
4–7	238	47	218	46
> 7	95	19	126	26
Cooked vegetables (portions per week)				
< 2	259	51	227	47
3	82	16	92	19
> 3	166	33	159	33

* The sum does not add up to the total because of some missing values.

with most findings[2–4,6]. In the Italian population the major sources of dietary iron are wine, vegetables and cereals[14,16]; this may explain the inverse association with iron intake, which may depend on components of these dietary items on AMI risk. However, it is difficult to disentangle the effects of these variables, even after adjustment in the multivariate analysis.

A limitation of this study is its case–control design, which might have caused some recall bias. However, cases and controls were interviewed in the same hospitals and came from the same geographical area. Furthermore patients admitted for chronic conditions or diseases

Table 2 Distribution of 507 cases of acute myocardial infarction (AMI) and 478 controls, and corresponding odds ratios (OR) with 95% confidence intervals (CI), according to dietary iron intake, Milan, Italy, 1995–1999

Approximate tertile of intake	AMI	Controls	OR (95% CI)*/χ^2 trend
Total dietary iron intake (mg day^{-1})			
< 12.10	173	155	1.00¶
12.10–15.37	173	155	0.89 (0.59–1.33)
> 15.37	161	168	0.48 (0.29–0.82)
χ^2 trend			6.90 ($P = 0.009$)
Haem iron intake (mg day^{-1})†			
< 3.83	180	149	1.00¶
3.83–5.12	165	164	0.78 (0.54–1.11)
> 5.12	162	165	0.71 (0.48–1.06)
χ^2 trend			2.81 ($P = 0.094$)
Non-haem, non-alcohol iron intake (mg day^{-1})‡			
< 6.69	178	153	1.00¶
6.69–8.33	156	168	0.69 (0.47–1.02)
> 8.33	173	157	0.80 (0.51–1.24)
χ^2 trend			1.02 ($P = 0.312$)
Intake of iron derived from alcoholic beverages (mg day^{-1})§			
< 0.18	175	159	1.00¶
0.18–2.39	165	154	0.84 (0.59–1.20)
> 2.39	167	165	0.60 (0.40–0.90)
χ^2 trend			6.20 ($P = 0.013$)

* OR were estimated from multiple unconditional logistic regression models including terms for age, sex, education, body mass index, cholesterol, smoking, coffee, non-alcohol energy intake, physical activity, history of hyperlipidaemia, diabetes and hypertension, and family history of AMI in first-degree relatives.
† Further adjusted for alcohol and vegetable intake.
‡ Further adjusted for alcohol and meat intake.
§ Further adjusted for meat and vegetable intake.
¶ Reference category.

https://doi.org/10.1079/PHN2005869 Published online by Cambridge University Press

related to known risk factors for AMI were excluded from the control group and participation was almost complete. The FFQ was satisfactorily valid and reproducible[11,12] and the potential confounding of several covariates, including energy intake, was allowed for in the analysis. No adjustment for lipoprotein fractions was possible, but it is unlikely that such allowance could materially modify the risk estimates. Since alcohol was a relevant source of iron intake in the Italian diet, allowance of total iron intake for alcohol may represent an overadjustment. We also had no information on iron fortification and supplementation, but this is very infrequent in Italy.

The ideal measure of iron status for epidemiological purposes is unclear[17]. Dietary iron may not accurately reflect total body iron, as gastrointestinal absorption varies depending on the iron status of the body and several other factors. Organic iron in the form of haemoglobin (haem iron) is absorbed more effectively than iron from cereals and vegetables (non-haem iron), and the absorption of inorganic iron is increased by ascorbic acid and modified by several diseases. However, also various serum measurements are strongly influenced not only by general iron status, but also by age, inflammation, cancer and liver disease.

A potential role for iron status in cardiovascular prevention has been related to its unfavourable effects on low-density lipoprotein, cholesterol and lipid oxidation, which could promote atherosclerotic processes[18,19]. However, carotid arterial intima-media thickening, a measure of early atherosclerosis, was not related to serum ferritin levels[20]; coronary stenosis and lesions were not related to serum iron, serum ferritin and transferrin levels[21,22]; and haemochromatosis was not associated with the development of atherosclerosis[23]. In Finnish men elevated serum ferritin concentration was associated with an excess risk of AMI mainly when serum low-density lipoprotein level was also high[1], and in Northern European and American populations iron intake may reflect consumption of haem iron and meat to a greater degree than in Italy, where non-haem sources of dietary iron are predominant[14].

Acknowledgements

This work was partly supported by the Ministero della Salute (contract no. 177, RF 2001). The authors thank MP Bonifacino for editorial assistance.

Conflict of interest: none declared.

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