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Determinants of ferritin and soluble transferrin receptors as iron status parameters in young adult women

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Abstract

Objective: To investigate associations between nutritional and non-nutritional variables and Fe status parameters, i.e. serum ferritin and soluble transferrin receptors (sTfR).

Design: Cross-sectional design. Fe status parameters were determined on a fasting venous blood sample. Nutritional variables were assessed using a 2 d food record and non-nutritional variables by a general questionnaire. A general linear model was used to investigate associations between the variables and Fe status parameters.

Setting: Region of Ghent, Dutch-speaking part of Belgium.

Subjects: Random sample of 788 women (aged 18–39 years).

Results: Median (interquartile range) ferritin and sTfR were 26·3 (15·9, 48·9) ng/ml and 1·11 (0·95, 1·30) mg/l, respectively. BMI and alcohol intake were positively associated and tea intake was negatively associated with serum ferritin. Women who used a non-hormonal intra-uterine device, who gave blood within the past year or who had been pregnant within the past year had lower serum ferritin values than their counterparts. Significant determinants of sTfR were smoking habit and pregnancy, with higher values for non-smokers and women who had been pregnant within the past year.

Conclusions: The present study indicates that contraceptive use, time since last blood donation, time since last pregnancy, BMI, alcohol and tea intake are determinants of Fe stores, whereas smoking habit and time since last pregnancy are determinants of tissue Fe needs. When developing strategies to improve Fe status, special attention should be given to women who use a non-hormonal intra-uterine device, gave blood within the past year and had been pregnant within the past year.

Keywords
Determinants
Iron status
Ferritin
Soluble transferrin receptors
Women

Adult women of childbearing age are at increased risk of Fe deficiency because of high Fe requirements due to menstrual blood losses or pregnancy[1]. According to an epidemiological study on Fe intake and Fe status carried out in 2002 at Ghent University, almost 20 % of young adult women were Fe-deficient (defined as serum ferritin $<15\,\mu g/l$ and Hb $\geq 12\,g/dl$)[2].

Body Fe content is maintained by a balance of Fe absorption and Fe losses. Since the body cannot actively excrete Fe, body Fe content must be regulated at the point of absorption. Fe stores and erythropoiesis are the main host-related factors that influence Fe absorption[3,4]. Apart from these host-related factors, the bioavailability of Fe depends also on its chemical form (haem Fe is better absorbed than non-haem Fe) and the presence of enhancers (e.g. vitamin C) and inhibitors (e.g. phytates) in the diet[4,5]. How this regulatory process is carried out on the molecular level is complex and still incompletely understood to date. In any case, this regulatory system of the body is limited and, beyond a critical point, Fe deficiency will develop[1].

In the present paper, the associations between nutritional and non-nutritional variables and parameters of Fe status, i.e. serum ferritin and soluble transferrin receptors (sTfR), are investigated in young adult women, as recommended by the Technical Consultation on the Assessment of Iron Status at the Population Level and others[6,7]. A better understanding of these determinants

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can be useful in developing strategies to improve Fe status in this particular group of the population.

Materials and methods

Study design

An epidemiological study on Fe intake and Fe status in young adult women (aged 18–39 years) was carried out in 2002 in Ghent, a medium-sized city (229 000 habitants) in the Dutch-speaking part of Belgium. Four thousand women were randomly selected from the population register of Ghent and were invited by postal mail to participate; 846 women out of 3480 (24 %) eligible women were included in the study. Non-eligible women were those who were pregnant (*n* 37), had moved (*n* 32), did not speak Dutch (*n* 9), were not able to come to the research centre (*n* 4) or were not able to volunteer within the envisaged period of the field work (*n* 14). Four hundred and twenty-four invitation letters were declared undeliverable by postal services and 2634 subjects were not prepared to participate. However, in the present study, only those participants were included for whom a blood sample was available (*n* 788).

The overall set of instruments used in the epidemiological study were: a newly developed and validated computerized Fe intake assessment tool[8]; an estimated 2 d food record (FR); a general questionnaire; a food knowledge questionnaire; and a fasting blood sample. Weight (kg) and height (m) were recorded under standardized conditions[9]. BMI was calculated as the ratio of weight to the square of height (kg/m^2). Data used in the present paper are based on the blood sample, the general questionnaire and the FR. Also, weight and height were used in order to calculate BMI.

Blood sample

To determine Fe status, a fasting venous blood sample was taken by a nurse at the home of the participant between 07.00 and 10.00 hours. The blood was then immediately transferred in cool boxes to the laboratory for analysis. Serum C-reactive protein (CRP), ferritin and sTfR were assayed by immunonephelometry on a BN II nephelometer (Siemens Healthcare Diagnostics, Deerfield, IL, USA) after the blood was clotted and centrifuged.

The general questionnaire and the 2 d FR were completed by the participants at their homes. These two instruments provided data on possible determinants (non-nutritional and nutritional) of serum ferritin and sTfR.

General questionnaire

Possible determinants collected by the general questionnaire were: age; highest educational level ('master or bachelor degree' and 'primary or secondary school'); smoking habit (current smoker yes or no); contraceptive use ('hormonal contraceptive' (including oral contraceptives and hormonal intra-uterine devices), 'non-hormonal intra-uterine device' and 'other or no contraceptive use'); physical activity ('health-enhancing physically active', 'minimally active' and 'inactive'); time since last blood donation ('<1 year' and '>1 year or non-blood donor'); and time since last pregnancy ('<1 year' and '>1 year or never been pregnant'). The level of physical activity was obtained by the short form of the International Physical Activity Questionnaire that was incorporated in the general questionnaire[10].

Food record

Data on possible nutritional determinants were collected by the 2 d FR: mean intakes of energy (kJ/d), haem Fe (mg/d), non-haem Fe (mg/d), Ca (mg/d), vitamin C (mg/d), alcohol (g/d), tea (g/d), coffee (g/d), red wine (g/d), milk and milk products (g/d), and meat, fish and poultry (g/d). Also data on the intake of Fe-containing supplements were gathered by the FR.

The FR was completed during two consecutive days. Information on the foods eaten (including brand names if possible) and the amount of food consumed was collected through an open entry format. The estimated amounts (e.g. pieces, coffee spoons) were then converted into weights on the basis of a standard protocol[11]. A nutritional software package (BECEL; Unilever, Rotterdam, The Netherlands) and different food composition tables (the Dutch food composition tables[12,13], the Belgian food composition tables[14,15] and the McCance and Widdowson food composition table[16]) were used for calculating nutrient intakes. The nutrient content of the foods was given 'as eaten', thus taking into account the changes due to preparation of the foods. Haem Fe was calculated according to the method of Monson *et al.*[17], assuming a haem Fe content of 40 % in animal tissues. Non-haem Fe was then calculated as the difference between total Fe and haem Fe. Information on the composition of the supplements was gathered mainly from the instructions for use or the package that women were asked to send with the diaries.

Statistical analyses

Statistical analyses were performed with the SPSS statistical software package version 12 (SPSS Inc., Chicago, IL, USA). Food and nutrient intakes were calculated as the mean of the 2 d intake period for all individuals. Spearman correlations were determined to investigate the associations of food and nutrient intakes, age and BMI with serum ferritin and sTfR respectively. A Kruskal–Wallis test was performed to investigate possible associations of categorical variables with serum ferritin and sTfR respectively. A general linear model was used to investigate possible independent associations of nutritional and non-nutritional determinants of the Fe status parameters serum ferritin and sTfR. Therefore two models were generated. The first model contained the non-nutritional determinants and nutrient intakes, and the second model contained the non-nutritional determinants, energy and food intakes. Nutrient and food intakes were not taken together in one model because of the

collinearity between some nutrients and foods. The validity of the models was checked by analyses of the residuals. Since the distribution of serum ferritin was skewed, the natural logarithm was used to increase normality. The χ^2 statistic was used to investigate whether the prevalence of Fe deficiency differed in different categories of contraceptive use, blood donation and pregnancy.

A P value of 0·05 was taken as the threshold for statistical significance.

Ethical approval

The study was approved by the Ethical Committee of Ghent University Hospital.

Results

Table 1 shows the number of individuals for whom specific data were available. Also, the table gives the median and interquartile range (IQR) for continuous variables and the proportion for categorical variables. Median age was 30 years and median BMI approximately 23 kg/m^2. Most women had a master or bachelor degree and most women were non-smokers. A hormonal contraceptive was the most chosen contraceptive. Women were quite equally divided across physical activity levels, with only slightly more individuals engaged in health-enhancing physical activity. Only 8 % of the women gave blood within the past year and 10 % had been pregnant within the past year. Fe-containing supplements were used by 9 % of the women. Median serum ferritin level was 26·3 ng/ml and sTfR 1·11 mg/l. Median energy intake was 8251 kJ/d (1972 kcal/d), haem Fe intake was less than 1 mg/d and non-haem Fe intake almost 10 mg/d. Median vitamin C and Ca intake was 87 mg/d and 902 mg/d, respectively. Median alcohol intake was 2 g/d, and red wine and tea intake was 0 mg/d. Median intakes of coffee, milk and milk products, and meat, fish and poultry were respectively 220 g/d, 217 g/d and 107 g/d.

Table 1 Characteristics of the study population: random sample of women aged 18–39 years (*n* 788) from Ghent, Belgium

Characteristic	Number	Median	IQR	Percentage
Ferritin (ng/ml)	770	26·3	15·9, 48·9	
sTfR (mg/l)	783	1·1	1·0, 1·3	
Non-nutritional determinants				
Age (years)	788	30·0	24·0, 35·0	
BMI (kg/m^2)	759	22·8	20·8, 25·4	
Education	762			
Master or bachelor degree				62·7
Primary or secondary school				37·3
Current smoker	763			
Yes				26·9
No				73·1
Contraceptive use	759			
Hormonal contraceptive				52·7
Non-hormonal intra-uterine device				8·8
Other or no contraceptive use				38·5
Physical activity	736			
Health-enhancing physically active				37·8
Minimally active				30·2
Inactive				32·1
Time since last blood donation	755			
<1 year				7·5
>1 year or non-blood donor				92·5
Time since last pregnancy	733			
<1 year				9·5
>1 year or never been pregnant				90·5
Fe-containing supplement use	614			
Yes				8·5
No				91·5
Dietary intakes	615			
Energy (kJ/d)		8251	6868, 9664	
Energy (kcal/d)		1972·1	1641·4, 2309·8	
Haem Fe (mg/d)		0·6	0·3, 1·0	
Non-haem Fe (mg/d)		9·8	8·3, 12·0	
Vitamin C (mg/d)		87·0	56·1, 130·7	
Ca (mg/d)		902·2	674·5, 1172·9	
Alcohol (g/d)		2·0	0·0, 12·5	
Red wine (g/d)		0·0	0·0, 0·0	
Coffee (g/d)		220·0	0·0, 379·0	
Tea (g/d)		0·0	0·0, 125·0	
Milk and milk products (g/d)		216·5	126·5, 356·5	
Meat, fish and poultry (g/d)		107·0	63·0, 150·0	

IQR, interquartile range; sTfR, soluble transferrin receptors.

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Table 2 Median ferritin (ng/ml) and sTfR (mg/l) in each category of education, smoking habit, contraceptive use, physical activity, blood donation, pregnancy and iron supplement use: random sample of women aged 18–39 years from Ghent, Belgium

	Ferritin (ng/ml)		sTfR (mg/l)	
	Median	*P* value	Median	*P* value
Education		0·185		0·536
Master or bachelor degree	27·7		1·11	
Primary or secondary school	23·7		1·10	
Current smoker		0·622		0·004
Yes	26·9		1·05	
No	26·3		1·12	
Contraceptive use		0·006		0·532
Hormonal contraceptive	26·7		1·12	
Non-hormonal intra-uterine device	20·1		1·06	
Other or no contraceptive use	26·9		1·10	
Physical activity		0·467		0·659
Health-enhancing physically active	26·4		1·11	
Minimally active	25·8		1·12	
Inactive	27·7		1·10	
Time since last blood donation		0·000		0·231
<1 year	20·2		1·15	
>1 year or non-blood donor	27·1		1·10	
Time since last pregnancy		0·009		0·001
<1 year	18·8		1·28	
>1 year or never been pregnant	26·7		1·10	
Fe-containing supplement use		0·659		0·831
Yes	28·3		1·11	
No	25·5		1·11	

sTfR, soluble transferrin receptors.

The median ferritin (ng/ml) and sTfR (mg/l) in each category of education, smoking habit, contraceptive use, physical activity, time since last blood donation, time since last pregnancy and Fe-containing supplement use is presented in Table 2. Significantly lower ferritin values were found in women who used a non-hormonal intra-uterine device, who gave blood within the past year and who had been pregnant within the past year. sTfR was significantly associated with smoking habit (lower values for smokers) and pregnancy (higher values for women who had been pregnant within the past year).

Based on the Spearman's correlation coefficients, significant positive associations were found between ferritin and age ($r = 0{\cdot}124$, $P = 0{\cdot}001$), BMI ($r = 0{\cdot}116$, $P = 0{\cdot}002$), haem Fe ($r = 0{\cdot}137$, $P = 0{\cdot}001$), alcohol ($r = 0{\cdot}135$, $P = 0{\cdot}001$) and coffee ($r = 0{\cdot}091$, $P = 0{\cdot}026$) intake. sTfR was positively associated with BMI ($r = 0{\cdot}079$, $P = 0{\cdot}030$) and negatively associated with Ca ($r = -0{\cdot}086$, $P = 0{\cdot}034$), alcohol ($r = -0{\cdot}107$, $P = 0{\cdot}008$) and coffee ($r = -0{\cdot}103$, $P = 0{\cdot}011$) intake.

Results of the general linear models with the natural logarithm of ferritin and sTfR respectively as dependent variables and the non-nutritional and nutritional determinants as independent variables are shown in Table 3 (nutrient intakes as nutritional determinants) and Table 4 (energy and food intakes as nutritional determinants). In Table 3, significant results were found for the association between ferritin and BMI, contraceptive use, time since last blood donation, time since last pregnancy and alcohol intake and for the association between sTfR and smoking habit and time since last pregnancy. In Table 4, the non-nutritional determinants significantly associated with serum ferritin were the same as those in Table 3. For sTfR, apart from smoking habit and time since last pregnancy, BMI was also significantly associated. No significant results were found between food intakes and ferritin and sTfR respectively.

Figure 1 illustrates the prevalence of Fe deficiency (serum ferritin <15 ng/ml) in different categories of contraceptive use, blood donation and pregnancy. Higher prevalences were found for women who use a non-hormonal intra-uterine device, who gave blood within the past year and who were pregnant within the past year (the latter not significant) compared with their counterparts.

Discussion

In order to investigate possible determinants of Fe status in young adult women, a good biomarker of Fe status must be chosen. Different laboratory measurements are available; however, no single method or combination of methods is suitable for all purposes. In the present study serum ferritin was used as a marker for Fe stores and sTfR as an indicator of tissue Fe deficiency. A limitation of serum ferritin is that it is elevated in response to infection or inflammation[1,7,18]. As CRP is a good marker of inflammation and to eliminate an influence on serum ferritin, participants with CRP values >3 mg/l (n 8) were excluded from the analyses. Also, women with elevated

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Table 3 Results of the general linear models with the non-nutritional determinants and nutrient intakes as independent variables and the natural logarithm of ferritin (ng/ml) and sTfR (mg/l) respectively as dependent variables: random sample of women aged 18–39 years from Ghent, Belgium

	Ln(ferritin; ng/ml)		sTfR (mg/l)	
	B	*P* value	*B*	*P* value
Age	0·008	0·210	0·002	0·551
BMI	0·030	0·001	0·007	0·071
Education				
Master or bachelor degree (ref)				
Primary or secondary school	−0·091	0·243	−0·028	0·454
Current smoker				
No (ref)				
Yes	0·062	0·442	−0·090	0·018
Contraceptive use				
Non-hormonal intra-uterine device (ref)				
Hormonal contraceptive	0·471	<0·001	−0·002	0·968
Other or no contraceptive use	0·334	0·008	0·033	0·585
Physical activity				
Health-enhancing physically active (ref)				
Minimally active	−0·112	0·180	0·031	0·437
Inactive	−0·063	0·450	−0·007	0·863
Time since last blood donation				
>1 year or non-blood donor (ref)				
<1 year	−0·503	<0·001	0·046	0·461
Time since last pregnancy				
>1 year or never been pregnant (ref)				
<1 year	−0·270	0·037	0·150	0·015
Fe-containing supplement use				
No (ref)				
Yes	0·116	0·372	−0·006	0·924
Energy (kcal/d)	<0·001	0·682	<0·001	0·774
Haem Fe (mg/d)	0·111	0·075	−0·035	0·230
Non-haem Fe (mg/d)	−0·002	0·894	0·005	0·314
Vitamin C (mg/d)	<0·001	0·594	<0·001	0·139
Ca (mg/d)	<0·001	0·640	<0·001	0·159
Alcohol (g/d)	0·007	0·009	−0·002	0·170
R^2 adjusted	0·086		0·026	

sTfR, soluble transferrin receptors; ref, reference category.

Table 4 Results of the general linear models with energy and food intakes as independent variables and the natural logarithm of ferritin (ng/ml) and sTfR (mg/l) respectively as dependent variables: random sample of women aged 18–39 years from Ghent, Belgium. The non-nutritional determinants are not provided as the results are the same as those found in the previous model

	Ln(ferritin; ng/ml)		sTfR (mg/l)	
	B	*P* value	*B*	*P* value
Energy (kcal/d)	<0·001	0·919	<0·001	0·683
Red wine (g/d)	0·001	0·183	<0·001	0·364
Coffee (g/d)	<0·001	0·497	<0·001	0·531
Tea (g/d)	<0·001	0·007	<0·001	0·088
Milk and milk products (g/d)	<0·001	0·154	<0·001	0·330
Meat, fish and poultry (g/d)	<0·001	0·701	<0·001	0·090
R^2 adjusted	0·089		0·028	

sTfR, soluble transferrin receptors.

ferritin values (>200 ng/ml) (*n* 2) were excluded because of a possible association with haemochromatosis and/or the metabolic syndrome, which could confound the results[19,20]. Another weakness of using serum ferritin as a marker of Fe status is its high day-to-day intra-individual variability. Four venous serum samples are required in order to estimate ferritin within 20 % of the true value, 95 % of the time[21]. For serum sTfR, only one is required[21]. sTfR seems to be less subject to within-person variability than ferritin. Since only one blood sample was available in the present study, the use of serum ferritin as a marker for Fe status could have influenced the results. A disadvantage of sTfR is its lack of standardization[7].

Another methodological consideration that has to be made concerns the estimation of food and nutrient intakes. To assess food and nutrient intakes, a 2 d food record was used. This method assesses intake over a short period of time and does not take into account the day-to-day variability of food consumption. It is thus no reflection of someone's 'usual' intake[22,23]. This will probably have an impact on the relationship between diet and Fe status parameters. Relationships in the present study will likely be underestimated, because there was only one blood sample to measure serum ferritin and because there were only 2 d to assess food and nutrient intakes. More blood samples and more food recording days would have made the distributions of ferritin values and food intake values narrower and would thus result in stronger relationships[24].

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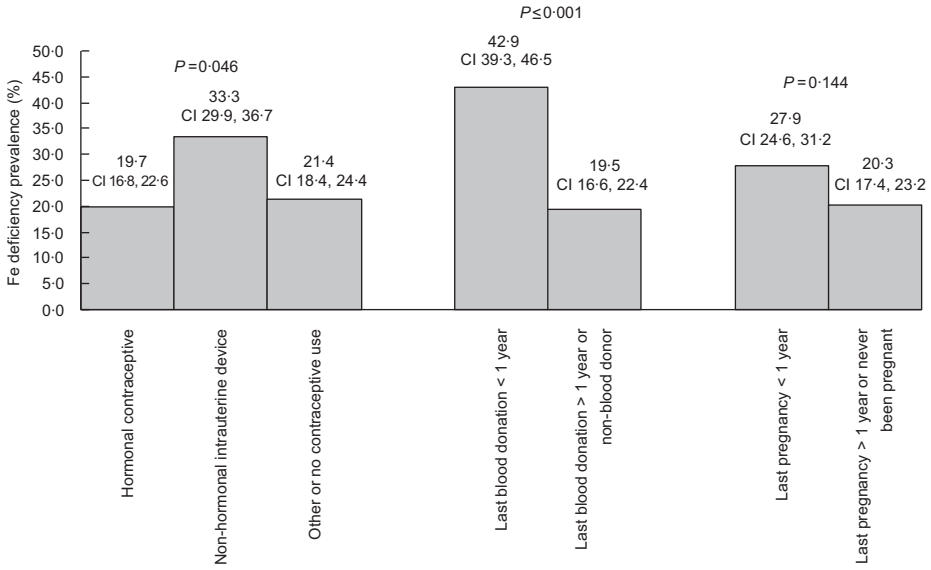

Fig. 1 Prevalence of iron deficiency (serum ferritin <15 ng/ml) in different categories of contraceptive use, blood donation and pregnancy: random sample of women aged 18–39 years from Ghent, Belgium. Differences between categories assessed using the χ^2 test

In the present study different nutrients and foods were included in the model that could have an effect on Fe status through an influence on Fe absorption. In the average Western diet, about 90–95 % of dietary Fe is non-haem Fe. However, up to one-third of totally absorbed Fe can be haem Fe, since haem Fe is more efficiently absorbed (25 %) than non-haem Fe (5–15 %)[4,25,26]. The proportion of dietary Fe that is absorbed is not only dependent on its chemical form, but also of the presence of enhancers and inhibitors. Therefore, vitamin C, alcohol and meat, fish and poultry intake (enhancers) and Ca, red wine, coffee and tea intake (inhibitors) were also included in the model to identify the determinants of Fe status[4,26–28].

Univariate analyses, not correcting for possible confounders, showed significant associations between serum ferritin and contraceptive use, time since last blood donation, time since last pregnancy, age and BMI as non-nutritional determinants and haem Fe, alcohol and coffee intake as nutritional determinants. After adjusting for confounders, contraceptive use, time since last blood donation, time since last pregnancy, BMI and alcohol intake remained significantly associated, and tea intake became significantly associated. However, the association found between serum ferritin and alcohol and tea intake should be taken with caution, because of the high proportion of women who did not drink alcohol (45 %) or tea (64 %) during the two recording days. For sTfR, univariate analyses, not correcting for possible confounders, showed significant associations with smoking habit, time since last pregnancy, BMI, Ca, alcohol and coffee intake. After adjusting for confounders, smoking habit and time since last pregnancy remained significantly associated. BMI was no longer significantly associated in the 'nutrient model' and borderline significantly associated in the 'food model'. No nutritional determinants were identified.

The association between serum ferritin and contraceptive use and the higher prevalence of women who used a non-hormonal intra-uterine device is probably related to the amount of blood loss. The use of non-hormonal intra-uterine devices induces high menstrual blood loss[29–31]. Hormonal contraceptives (including oral contraceptives and hormonal intra-uterine devices) have been demonstrated to decrease menstrual bleeding[32–34].

Also related to blood loss are the lower ferritin values and higher Fe deficiency prevalence found in women who gave blood within the past year.

It is thought that the risk of Fe deficiency is low in the postpartum period, since Fe status is expected to improve after delivery (contraction of the expanded red cell mass, decline of maternal Fe requirements, decrease of Fe losses by postpartum amenorrhoea)[35]. However, it seems that postpartum Fe deficiency is far more common. Potential risk factors include e.g. complications associated with high blood losses, lack of prenatal Fe supplementation, delivering of multiple fetuses, not exclusively breast-feeding or short duration of breast-feeding[35]. This is in line with the results of the present study, since women who had been pregnant during the past year had lower ferritin values and higher sTfR values than their counterparts. Moreover, the prevalence of women with Fe deficiency was higher (however not significant) in women who were pregnant during the past year.

Comparisons between the present study and studies in the literature need to be interpreted with caution because of different study designs, methodologies and populations.

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In the literature there is no consistency concerning the determinants of serum ferritin concentrations. A study in 2200 British women (aged 35–69 years) demonstrated a positive association between ferritin and intakes of haem Fe, red and white meat, vitamin C and alcohol, age and BMI. Negative associations were found for energy and blood donation. No associations were found for intakes of total Fe, non-haem Fe, Ca and fish and for smoking habit and Fe supplement use[36]. In the SU.VI.MAX study in France in more than 3000 women (aged 35–60 years), Ca intake, dairy product intake and the use of an intra-uterine device were negatively associated and oral contraception, total dietary Fe, meat and fish intake were positively associated with serum ferritin concentrations. No significant associations were found for haem Fe, vitamin C, coffee and tea intake[37]. Another study in 1108 subjects between 6 months and 97 years old, in the Paris area, showed (after adjustment for age, sex and inflammation) significant positive associations of serum ferritin with haem Fe and non-haem Fe intake and negative associations with Ca intake. Coffee, tea or vitamin C intake was not significantly associated[38]. In 222 Dutch adult women (aged 20–79 years), regression analyses showed positive associations between serum ferritin and age, haem Fe, meat, wine and alcohol intake and negative associations with energy intake and blood donation[39]. In 125 rural Mexican women (aged 16–44 years), time since birth of the last child, ascorbic acid intake and non-haem Fe intake (but not haem Fe intake) were positive determinants of serum ferritin. BMI and age were not significantly associated[40]. Raya *et al.*[41] investigated biological variation factors of sTfR in 409 women (aged 3–91 years) and found significant associations for age and for tobacco use in females $\leq$20 years old and physical activity in females $>$20 years old.

The general linear models in the present study showed low values for adjusted R^2, indicating that the variables in the model do not explain much of the variance in serum ferritin and sTfR respectively and that perhaps other variables are important or associations are underestimated. Another determinant of serum ferritin that could not be investigated in the present study is menstrual blood loss. According to Harvey *et al.*[42], who investigated the impact of menstrual blood loss and diet on Fe status among women in the UK, the amount of menstrual blood loss seemed to be the most important predictor of Fe stores.

To conclude, the present study indicates that contraceptive use, time since last blood donation, time since last pregnancy, BMI, alcohol and tea intake are determinants of Fe stores, whereas smoking habit and time since last pregnancy are determinants of tissue Fe needs. Since also higher prevalences of Fe deficiency were found in women who used a non-hormonal intra-uterine device, who gave blood within the past year and who were pregnant within the past year, special attention should be given to these women when developing strategies to improve Fe status.

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