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Prevalence of iron deficiency in 12-mo-old infants from 11 European areas and influence of dietary factors on iron status (Euro-Growth study)

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A prospective longitudinal cohort study was performed to assess the prevalence of iron deficiency in European infants at 12 mo of age, and to study the influence of socio-economic status, dietary factors, growth and morbidity on iron status. The cohort consisted of 488 normal term infants from primary healthcare centres in 11 European areas. Assessed were socio-economic variables, dietary intake, anthropometry and morbidity at regular intervals from birth to 12 mo, and haemoglobin, serum ferritin, mean corpuscular volume, transferrin saturation and serum transferrin receptor concentrations at age 12 mo. The prevalence of anaemia was 9.4%, of iron deficiency 7.2%, and of iron deficiency anaemia 2.3%. More than 40% of anaemia was associated with normal iron status and associated with an increased frequency of recent infections. Iron deficiency anaemia was significantly more frequent with low (5.1%) than high socio-economic status (0%). Dietary factors accounted for most of this variation in multiple regression analysis. Early introduction of cows' milk was the strongest negative determinant of iron status. Feeding of iron-fortified formula was the main factor positively influencing iron status. Other dietary factors, including breastfeeding, did not play a significant role as determinants of iron status at age 12 mo.

Conclusion. Iron deficiency anaemia is present in 2.3% of 12-mo-old European infants. The prevalence of iron deficiency anaemia varies strongly with socio-economic status. Avoidance of cows' milk feeding during the first year of life is the key measure in the prevention of iron deficiency.

Key words: *Anaemia, dietary factors, growth, iron deficiency, socio-economic status*

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Infants and young children are at particular risk of iron deficiency due to high demands for iron during a period of rapid growth and because their diet is often low in available iron. Iron reserves of the healthy, term newborn usually ensure an adequate supply of iron for the first 4–6 mo of life. After 6 mo of age the infant becomes critically dependent on dietary iron. Therefore, iron deficiency develops most commonly in late infancy and during the second year of life (1). Iron deficiency that progresses to the stage of iron deficiency anaemia may impair mental and psychomotor development and possibly growth (2).

Studies in the United States have reported a considerable decline in the prevalence of iron deficiency in early childhood over the past two decades—a decline that has been attributed to improved feeding practices and preventive programmes (3, 4). Only scattered reports on the prevalence of iron deficiency exist from European countries (5–10). However, reported prevalences vary, largely due to differences in study populations, differing feeding practices and varying criteria from one study to the next for the definition of iron deficiency.

Only a few European studies have been based on representative samples of the general childhood population and these report prevalences of iron deficiency ranging from 9% to 34% and prevalences of iron deficiency anaemia ranging from 3% to 8% in children aged 1 to 2 y (6–10). Studies performed in socio-

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economically disadvantaged population segments observed much higher prevalences of iron deficiency, a fact which is attributed to low food quality and lack of education about infant feeding (5, 6).

Prevalences of iron deficiency vary as a function of dietary factors such as early feeding of cows' milk (11), the use of iron-fortified infant formulas (12, 13) and the time of introduction, iron-content and iron-bioavailability of weaning foods (14). The relative importance of these factors as determinants of iron status is not well established and likely varies between different populations.

The Euro-Growth study was a prospective longitudinal multicentre cohort study of growth in normal European children from birth to 36 mo of age. In a substudy, iron status was determined in infants at 12 mo of age with the objectives: (i) to assess the prevalence of iron deficiency and iron deficiency anaemia in a representative sample of European infants and (ii) to study the influence of socio-economic status, dietary factors, growth and morbidity on iron status.

Subjects and methods

Study design

The Euro-Growth study was designed as a prospective longitudinal multicentre cohort study. Normal infants ($n = 2245$) from 22 European centres were followed from birth to age 36 mo. Study design, demographic characteristics of the study population and growth have been described in detail elsewhere (15). Study centres were based at well-baby clinics, paediatric offices or paediatric hospitals. Parents were approached to participate during the post-partum period at the maternity ward or when first attending the well-baby clinic. The areas from which study populations were drawn coincided with the catchment areas of participating institutions.

Iron study

Eleven Euro-Growth study centres (Athens, Bilbao, Budapest, Dublin, Madrid, Naples, Porto, Rostock, Santiago, Umeå, Vienna) agreed to invite parents to participate in the 'Iron Study'. Parents of 533 infants consented to blood testing for iron status at 12 mo of age. This represented 42% of the 1269 infants examined in the 11 participating centres at this age. The number of infants per centre ranged from 12 (Rostock) to 92 (Dublin). Written informed consent was obtained from parents and the study protocol was approved by the Ethics Committee of each study centre.

To assess selectivity in participation in the study, a non-participation analysis was performed comparing demographic factors between (i) participants of the Euro-Growth study and non-participants from the background population and (ii) subjects participating in the iron study and Euro-Growth subjects not participating in the iron study. For the overall Euro-Growth study, the analysis showed that weight and height of mothers and gender and birthweight of the infants were not associated with participation, while age and educational level of participating mothers was increased compared to the background population. There were differences between study centres with respect to selectivity in participation (15). For subjects in the iron study, all demographic factors were similar to the Euro-Growth study population, except for a higher maternal age in participants of the iron study (28.4 (4.9) vs 27.4 (5.0) y, mean (SD), $p < 0.001$).

Study population

Infants were recruited to the Euro-Growth study between January 1991 and April 1993. Inclusion criteria were: birthweight $\geq$2500 g, gestational age $\geq$37 wk, single birth, Caucasian origin, no language barrier with parents, known father, and high probability of successful participation for 36 mo. Exclusion criteria were maternal gestational diabetes, chronic disease during pregnancy, genetic disease, major malformation and neonatal illness requiring more than 7 d of hospitalization.

Study procedures

Infants were enrolled in Euro-Growth within 30 d of birth. Parents were interviewed at the time of enrolment to obtain information on baseline demographic factors. Birthweight and length and complications at birth were recorded. Study visits occurred within 4 d of age 30, 60, 91, 122, 153, 183 d, and within 14 d of age 274 and 365 d. At each visit, dietary practices were assessed by semi-quantitative recall. Full breastfeeding (no other milk than breastmilk) and partial breastfeeding, formula feeding, cows' milk feeding, intake of cereals, fruits, vegetables and meat were recorded. Iron-fortification levels of infant formulas ranged between 5 and 14 mg/L. All commercially prepared cereals were iron fortified. Oral iron supplements were recorded as given to infants by their primary physician according to local standards of practice. Type and duration of illnesses were recorded. Anthropometry was performed by trained examiners following a standardized protocol.

Iron status

Blood was obtained within 14 d of age 365 d of age by venous (8 centres) or capillary sampling (3 centres). Infants with a history of infection during the previous 90 d were included, but infection was accounted for in the regression analyses. Hb and MCV were measured by Coulter Counter at study centres. Serum was separated by centrifugation, frozen and shipped in batches to Vienna for analysis. Serum ferritin concentration (SF) was analysed by radioimmunoassay (RIAgnost R Ferritin, Behring, Marburg, Germany), serum iron was measured colorimetrically (Ektachem, Kodak

Table 1. Haemoglobin and indicators of iron status in European infants at 12 mo of age ($n = 488$).

Parameter		Girls ($n = 227$)		Boys ($n = 261$)	
		Mean (SD)	Median (p5–p95)	mean (SD)	median (p5–p95)
Haemoglobin	g/L	121 (8)	120 (108–134)	120 (9)	120 (106–136)
Mean corpuscular volume	fl	78 (4)	78 (71–85)	77 (5)	78 (69–85)
Serum ferritin	μg/L	25 (21)	19 (4–63)	22 (15)	19 (4–55)
Transferrin saturation	%	23 (13)	21 (7–42)	22 (12)	21 (5–48)
Serum transferrin receptor	mg/L	3.1 (0.8)	3.0 (2.0–4.5)	3.3 (1.0)	3.2 (2.2–4.9)

Abbreviations: p5, p95, percentiles.

Clinical Chemistry Products) and transferrin concentration by immunodiffusion (NOR-Partigen Transferrin, Behring). Total iron binding capacity was calculated from transferrin × 1.25, and transferrin saturation (TSAT) was calculated as serum iron × 100 / total iron binding capacity. Serum transferrin receptor concentration (TfR) was assayed by enzyme-linked immunoassay (Quantikine, Human TfR Immunoassay, R&D Systems, Minneapolis, MN, USA). For SF and TfR assays, control sera provided by the manufacturers were tested in each run. Analyses were considered valid if control values fell within the established ranges.

Anaemia was defined as a Hb below 110 g/L, and cut-off values used for MCV were <70 fl, for SF <10 μg/L and for TSAT <10% (16). The upper limit of 4.4 mg/L for TfR was derived (95th percentile) from those study subjects who had normal values for Hb, MCV, SF and TSAT ($n = 330$). Iron deficiency was defined as the presence of two or more abnormal values of the four iron status indicators, MCV, SF, TSAT, TfR. Iron deficiency anaemia was defined as anaemia plus two or more abnormal iron status indicators (17). The ratio of TfR/SF was calculated which had been reported to represent the best single measure of iron status (18).

Statistical analysis

Data were computerized at study centres using Epi Info software (Center for Disease Control and Prevention, Atlanta, Georgia, USA) and pooled after data quality control at Nijmegen University, The Netherlands. The Statistical Program for Social Sciences (SPSS, MC Chicago, IL) was used for analysis. Serum ferritin and TfR were log-transformed and TSAT square-root transformed to achieve normal distributions. *T*-test, analysis of variance and the chi-squared test were used for group comparison.

Stepwise multiple regression analysis was applied to study the associations of Hb, MCV, SF, TSAT and TfR as dependent variables with the following independent variables: maternal age and educational level; gender of the infant, birthweight, weight gain and length gain between age 0 and 12 mo, infectious illnesses lasting ≥3 d between age 9 and 12 mo of age (yes/no); full or partial breastfeeding, formula, cows' milk (duration of feeding between age 0–12 mo), consumption of cereals, fruits and vegetables, meat between age 9 and 12 mo (never/1–2 times weekly/almost daily) and iron supplements between 9 and 12 mo (yes/no). Stepwise logistic regression analysis was applied to evaluate the risk of developing anaemia, iron deficiency and iron deficiency anaemia associated with the same independent variables.

Results

Data presented in this report pertain to 488 infants (92% of infants enrolled) on whom data on Hb and 3 or more indicators of iron status were available. Haemoglobin and iron status indicators are summarized in Table 1. Prevalences of abnormal values and of iron deficiency and iron deficiency anaemia are presented in Table 2.

Table 2. Prevalences of anaemia, abnormal iron indicators, iron deficiency and iron deficiency anaemia in European infants.

Deficiency	Cut-off value	Total ($n = 488$) % (n)	Girls ($n = 227$) % (n)	Boys ($n = 261$) % (n)
Anaemia	Haemoglobin < 110 g/L	9.4 (46)	7.0 (16)	11.5 (30)
Low mean corpuscular volume	< 70 fl	4.6 (22)	2.3 (5)$^+$	6.7 (17)$^+$
Low serum ferritin	< 10 μg/L	15.6 (76)	12.8 (29)	18.0 (47)
Low transferrin saturation	< 10%	15.0 (67)	13.5 (28)	16.3 (39)
High serum transferrin receptor	> 4.4 mg/L	8.4 (41)	6.6 (15)	10.0 (26)
Iron deficiency[1]		7.2 (35)	4.8 (11)	9.2 (24)
Iron deficiency anaemia[2]		2.3 (11)	1.3 (3)	3.1 (8)

[1] Two or more iron indicators abnormal (mean corpuscular volume, serum ferritin, transferrin saturation, serum transferrin receptor).
[2] Haemoglobin plus two or more iron indicators abnormal.
$^+ p = 0.02$.

Table 3. Dietary and infant-related factors significantly associated with haemoglobin, mean corpuscular volume (MCV), serum ferritin (SF), transferrin saturation (TSAT) and serum transferrin receptor (TfR) concentrations (multiple regression models).

	Standardized partial regression coefficients (beta)				
Determinants	Haemoglobin	MCV	log (SF)	√ TSAT	log (TfR)
Cows' milk[1]	−0.20***	−0.14**	−0.10*	−0.19***	0.28***
Formula[1]	0.15**	0.18***	0.23***	0.16***	
Cereals[2]		0.13**	0.22***		0.10*
Iron supplements[3]		−0.10*	0.13**		−0.15***
Male gender		−0.09*	−0.09*		
Birth weight (g)			0.20***		
Weight gain (kg/12 mo)	0.21***				0.13**
Length gain (cm/12 mo)			−0.09*		
R^2 (adjusted)	0.13	0.11	0.14	0.08	0.11
F-ratio	25.0***	12.8***	14.0***	20.4***	14.9***
n	471	458	471	431	470

[1] Duration (months) of feeding; [2] feeding between ages 9 and 12 mo (never/1–2 weekly/daily); [3] given between 9 and 12 mo (no/yes); *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

The overall prevalence of anaemia was 9.4%, of iron deficiency 7.2% and of iron deficiency anaemia 2.3%. Although mean values of Hb and iron status indicators did not suggest gender-related differences (Table 1), prevalences of abnormal values of all parameters tended to be higher in boys, which reached statistical significance for MCV (Table 2). More severe anaemia (Hb <100 g/L) was also significantly more frequent in boys (2.7%) than in girls (0%; $p = 0.02$). Between study centres, prevalences of anaemia ranged from 0% to 41%, of iron deficiency from 0% to 33%, and of iron deficiency anaemia from 0% to 12%. Limiting the analysis to six centres with larger subsamples ($n \geq 36$, total $n = 412$), prevalences of anaemia were 7.6% (mean, range 0–15%), of iron deficiency 5.6% (1.5–11%), and of iron deficiency anaemia 1.5% (0–3%). Iron status data from two study centres have been reported in more detail elsewhere (19, 20).

Among infants with anaemia, only 24% had two or more abnormal iron indicators, as iron deficiency anaemia was defined, 35% had one abnormal iron indicator and 41% of anaemic infants had all iron indicators normal. A history of recent infections was present in 78% of the latter group, compared to 56% and 36% anaemic infants with one abnormal iron indicator and children with iron deficiency, respectively ($p = 0.08$).

The prevalence of anaemia in infants of mothers with primary ($n = 117$), secondary ($n = 283$) and university ($n = 73$) education were 16.2%, 7.4% and 6.8%, respectively ($p = 0.02$). Corresponding prevalences of iron deficiency were 7.7%, 8.1% and 1.4% ($p = 0.12$) and of iron deficiency anaemia 5.1%, 1.8% and 0% ($p = 0.04$).

Dietary practices and growth of infants enrolled in the iron study were similar to those in the total Euro-Growth cohort and are reported in detail elsewhere (21, 22). Since dietary factors proved to be important predictors of iron status, these are summarized briefly. Infants in the iron study were fully breastfed for an average of 1.6 mo (SD 1.9, range 0–7) and partially breastfed for 3.6 mo (SD 3.9, range 0–12). Twenty-five percent of infants received formula from birth. Mean duration of formula feeding was 7.9 mo (SD 3.9, range 0–12). Mean age at introduction of cows' milk was 10.0 mo (SD 2.6, range 1–12). At 12 mo, about half of the infants were fed follow-on formula and a similar proportion was receiving cows' milk on a daily basis. Between ages 9 and 12 mo, 91% of infants consumed meat almost every day. Eleven percent of infants received oral iron supplements between 9 and 12 mo.

Multiple regression analysis was employed to test associations between Hb, SF, MCV, TSAT, TfR as dependent variables and demographic and dietary factors, growth and morbidity as independent variables. The best fitting models for each dependent variable are presented in Table 3. The duration of feeding cows' milk had the strongest and most consistent negative influence on Hb and iron status indicators. For example, for every month of cows' milk feeding there was an average decrease of 2 g/L in Hb at 12 mo. The duration of formula feeding was positively associated with four of the five parameters examined. Positive associations were also found for the consumption of cereals and use of iron supplements. Birthweight was positively associated with SF, whereas length gain from birth to 12 mo was negatively associated with SF. Weight gain was positively associated with TfR and, surprisingly, also with Hb. A model using the TfR/SF ratio as dependent variable revealed similar associations with dietary and growth variables as with TfR and SF separately (data not shown). The regression models explained between 8% and 14% of the variance of iron status indicators.

Stepwise logistic regression tested the risk of developing anaemia, iron deficiency and iron deficiency anaemia asssociated with the same independent vari-

Table 4. Dietary and infant-related factors significantly associated with the risk of anaemia, iron deficiency and iron deficiency anaemia[1] (logistic regression models).

Determinants	Odds ratios (95% confidence intervals)		
	Anaemia	Iron deficiency	Iron deficiency anaemia
Cows' milk[2]	1.23*** (1.10–1.38)	1.18** (1.05–1.35)	1.39*** (1.14–1.69)
Formula[2]		0.89* (0.81–0.98)	
Iron supplements[3]	0.34** (0.16–0.75)		
Male gender	2.08* (1.02–4.25)		
Weight gain (kg/12 mo)	0.58** (0.40–0.83)		
Maternal education[4]			0.27* (0.08–0.87)
χ^2	38.4***	19.8***	35.6***
n	471	471	471

[1] Definitions of deficiencies as in Table 2; [2] duration of feeding (months); [3] given between ages 9 and 12 mo (no/yes); [4] maternal educational status (primary/secondary/university).
*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

ables (Table 4). Feeding of cows' milk was again the most consistent risk factor negatively influencing iron status. Each month of cows' milk feeding increased the risk of anaemia, iron deficiency and iron deficiency anaemia by 23%, 18% and 39%, respectively. Formula feeding was associated with a decreased risk of iron deficiency. Weight gain and use of iron supplements were associated with a decreased risk of anaemia, male gender with an increased risk of anaemia. High maternal educational status was associated with a decreased risk of iron deficiency anaemia.

Discussion

This is the first study evaluating iron nutritional status at 12 mo of age across multiple European countries. The study prospectively and longitudinally assessed factors with potential influence on iron status. The study population represents a well-defined cohort of normal infants born in the first half of the 1990s. Demographic characteristics of the sample were representative for the local background populations except for a slightly increased maternal age and maternal education. There was variability between study centres in demographic factors as well as iron status, reflecting regional differences and to some extent selectivity in participation. However, the pooled sample provides a good estimate of iron status in average Euro-Growth infants. For the objective to identify determinants of iron status, the variability of demographic and dietary factors across multiple centres is an advantage, as relationships with iron status become more readily detectable.

Prevalences of anaemia, iron deficiency and iron deficiency anaemia in this cohort were 9.4%, 7.2% and 2.3%, respectively. These prevalences were lower than those reported from recent population-based studies of infants in the United Kingdom (8, 10), France (6) and Spain (7), which is likely due to different selections of study populations in terms of socio-economic status and morbidity. The largest population-based study in children aged 1–2 y is the NHANES III survey, performed in the USA during 1988–94 which reported prevalences of 9% for iron deficiency and 3% for iron deficiency anaemia (4). Corresponding prevalences in the European cohort were lower, probably reflecting demographic differences and also differences in methods between the two studies, such as the number, types and assays used for iron indicators.

Of infants with anaemia, only one quarter had definite iron deficiency anaemia, one-third had one abnormal iron indicator and 41% of anaemic infants had all iron indicators normal. This last group had an increased frequency of recent infection (78%), the most common cause of anaemia next to iron deficiency at this age (23). However, among anaemic children with one, and two or more abnormal iron indicators, 56% and 36% had a history of recent infection, respectively. The data suggest that iron deficiency anaemia and anaemia of infection frequently coexist and are difficult to discriminate based on iron indicators. Following infections, SF may be spuriously increased, which may partially account for the proportion of children with indeterminate iron status. A diagnostic improvement is the use of the TfR, a sensitive indicator of iron deficiency that is independent of infection (18). However, the interpretation of TfR data is limited by qualitative differences and lack of standardization between currently available assays (24). Unfortunately, infection reactants were not obtained in this study.

The second objective of the current study was to examine the influence of socio-economic, dietary factors and growth on iron status. Educational status of the mother was used as indicator of socio-economic status. Stratifying for this factor revealed a significantly increased prevalence of iron deficiency anaemia in infants of mothers with only primary education compared to infants of mothers with university education. This risk was mainly determined by feeding practices. However, when controlling for dietary factors in logistic regression, maternal education remained significantly associated with iron deficiency anaemia. Thus, other factors related to socio-economic status, e.g. access to medical care, influence iron status.

The most important dietary factor was early introduction of cows' milk, a factor which had a clear negative influence on iron status at 12 mo of age. Cows' milk is a poor source of iron and also reduces the bioavailability of iron provided by other foods (25). Occult gastrointestinal blood loss provoked by cows' milk may also contribute to the risk of iron deficiency (26). The negative influence of cows' milk on iron status has been demonstrated previously (7, 11, 27). The results of the present study illustrate the singular importance of cows' milk compared to other dietary factors. In spite of recommendations (28) to avoid unmodified cows' milk before the age of 12 mo, cows' milk evidently still plays a major role in infant feeding in certain areas and population subgroups.

The most important factor positively associated with iron status was the duration of feeding of iron-fortified formula. Formula feeding most strongly influenced SF, which reflects iron stores. Formula feeding was also positively correlated with Hb and MCV and a decreased risk of iron deficiency. Several studies have shown that iron-fortified formulas are effective in preventing iron deficiency during the first year of life and beyond (12, 29). These earlier studies have used formulas with high iron fortification levels of 12–15 mg/L. In the present study, formulas with an average iron level of 7–8 mg/L, as currently available in Europe, were protective against iron deficiency, which is consistent with recent experimental studies (13).

Other dietary factors played a minor role as predictors of iron status in our regression models. Breastfeeding was found to have little impact on iron status at 12 mo of age, probably because breastfeeding was largely confined to the first 6 mo of life in this cohort. Feeding iron-fortified cereals between 9 and 12 mo showed some influence on SF and MCV levels, but was not associated with increased Hb or a decreased risk of iron deficiency anaemia. Intake of meat and fruits and vegetables did not explain any of the variation in iron status, which is probably due to the relatively uniform and almost universal use of these beikost items (>90%) between 9 and 12 mo in this cohort.

The iron content of the fetus is closely related to body weight, therefore birthweight determines iron endowment for the first months of life (30). Birthweight was found to significantly predict iron stores as late as 12 mo in our study. Length gain until 12 mo was inversely related to SF levels, which may reflect more rapid utilization of iron stores due to greater iron needs for growth in faster growing infants (9, 10). Conversely, there was a positive association between weight gain and Hb, consistent with previous reports (10). Increased Hb in spite of decreased SF in fast growing infants indicates that their iron stores are not exhausted beyond sufficiency.

The negative association between male gender and MCV and SF values, which has previously been described (10), may partially be explained by the faster growth rate observed in boys (22). The increased risk of anaemia in boys, however, cannot be explained by growth and may reflect physiologic differences between genders.

In conclusion, iron deficiency anaemia was found in 2.3% of normal 12-mo-old European infants. The prevalence of iron deficiency anaemia varies strongly with socio-economic status, an effect mainly determined by dietary factors. Avoidance of cows' milk feeding in the second half year of life is the key measure in the prevention of iron deficiency.

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