Prevalence and Risk Factors of Iron Deficiency in Healthy Young Children in the Southwestern Netherlands

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ABSTRACT

Objectives: Iron deficiency (ID) and iron deficiency anemia (IDA), during the first years of life, are associated with delayed motor and neurological development. Many studies evaluated iron status without an assessment of an acute-phase protein to identify infection. Because most indicators of iron status are influenced by infection, these data may underestimate the ID prevalence. A food consumption survey in the Netherlands showed that the mean iron intake of children ages 2 to 3 years was below the advised adequate intake of 7 mg/day. The aim of the study was to investigate iron status in a well-defined, healthy population of young children in the southwestern region of the Netherlands and to identify risk factors for ID.

Methods: We conducted a multicenter, observational study in healthy children ages 0.5 to 3 years. We defined ID as ferritin <12 μg/L and IDA when, in addition, hemoglobin was <110 g/L. Children with elevated C-reactive protein levels (>5 mg/L) or underlying causes for anemia were excluded. Parents filled in a questionnaire to identify risk factors for ID.

Results: We included 400 children in the study. ID and IDA were detected in 18.8% and 8.5% of the children, respectively. The present use of formula and the visit of preschool/day care were associated with a lower prevalence of ID, and a high intake of cow's milk was associated with a higher prevalence of ID, after adjustment for age.

Conclusions: ID is present in 18.8% of healthy children ages 0.5 to 3 years and living in the southwestern region of the Netherlands. The present visit of preschool/day care and the use of formula are associated with a reduced risk of ID, whereas a high intake of cow's milk is associated with an increased risk of ID.

Key Words: anemia, day care, follow-on formula, preschool

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Iron is involved in oxygen transport and energy metabolism and plays an important role in brain development. Young children are vulnerable to the effects of iron deficiency (ID) because of the rapid growth and development of their brain and other organs that occur from birth to the age of 3 years (1). Increasing evidence suggests that even ID in the absence of iron deficiency anemia (IDA) can have a long-term detrimental influence on mental, psychomotor, and behavioral development (2–4); however, iron supplementation of iron-replete children may have adverse effects, such as increased risk of infections, impaired growth, and cognitive development (5,6). The therapeutic range of iron is small and, therefore, it is important to prevent both the ID and the iron overload (7). ID is common in young children in most Western countries; however, large disparities in the prevalence of ID exist, ranging from 0% (7) to 85% (8) in Europe and 7% to 21% in the United States (9). The differences in ethnicity, socioeconomic status (SES), and dietary iron intake account for most of this variation. Reported iron intake in young children is considerably lower in Europe (4.7–11.5 mg/day) (10) than in the United States (15.8 mg/day) (11). A large food consumption survey in the Netherlands in 2005–2006 showed that the mean iron intake in children ages 2 to 3 years was 6.1 mg/day, which was below the advised intake of 7 mg/day (12). Therefore, we hypothesized that ID would be a common problem in these children. Many studies have evaluated iron status without an assessment of an acute-phase protein to identify infection (9,13). Because most indicators of iron status increase in the presence of infection or inflammation, these data may underestimate the prevalence of ID (14). To our knowledge, this is the largest prospective observational study on iron status, with an extensive evaluation of the risk factors for ID, in a well-defined, healthy population of children ages 0.5 to 3 years.

METHODS

Study Subjects

We conducted a multicenter, observational study that included healthy children ages 0.5 to 3 years undergoing general anesthesia for simple elective surgery or a diagnostic procedure. Children were recruited in the Juliana Children's Hospital from January 2011 to May 2012 and in the Sophia Children's Hospital from September 2011 to January 2012. The Juliana Children's Hospital is a large secondary hospital in The Hague and Sophia Children's Hospital is a tertiary hospital in Rotterdam. Together these hospitals serve as the main pediatric referral hospitals for the southwestern region of the Netherlands (province of Brabant, Zeeland, and Zuid-Holland). During a preoperative screening, an extensive medical history and a physical examination were performed by a pediatric anesthesiologist and an experienced resident pediatrician and included only healthy children. The exclusion criteria were known infections during the last 4 weeks, the use of iron supplementation during the last 6 weeks, blood transfusion during the last 6 months, preterm birth before 32 weeks' gestational age (GA), known hemoglobinopathies, oncologic disorders, multiple congenital malformations, and metabolic diseases. Children referred for adenotomy or tonsillectomy were not included because the prevalence of upper airway infections in these children is high (15). A written informed consent was obtained by the investigators (L.U., J.V., and P.P.T.) before the surgery. The study was approved by the medical ethics committee of southwest Holland.

Study Design

All of the children received a peripheral venous catheter to administer anesthetics. During insertion of the catheter, venous blood (2 mL) was collected and analyzed for hemoglobin (Hb), mean corpuscular volume (MCV), ferritin, and C-reactive protein (CRP). CRP was measured to detect an infection, which usually is accompanied by an increase in ferritin. Children with an elevated CRP ($\geq$5 mg/L) were excluded from the study. We defined ID as ferritin <12 μg/L and IDA as Hb <110 g/L (<6.8 mmol/L) combined with ID, according to the criteria of the World Health Organization (WHO) (16).

When ID or IDA was established, the children were treated with iron supplementation (oral ferrous fumarate 2.9 $mg \cdot kg^{-1} \cdot day^{-1}$). After 2 months of treatment a control blood sample was taken. If ID persisted after the iron supplementation or anemia persisted with a normal iron status, other causes of anemia and/or ID were investigated. The children who were found to have other causes of ID or anemia were excluded from the study.

After the inclusion, parents were interviewed about the child's diet by 1 of the authors (L.U., J.V., or P.P.T.). Questions concerned the age of the child at which breast-feeding had stopped and introduction, duration, and amount of formula feeding and/or cow's milk. The period of breast-feeding was defined as the period from birth onward during which the child received breast milk exclusively or in a combination with formula feeding or cow's milk. The average intake of fruits, vegetables, bread, meat, or fish was estimated by means of photographs showing 3 different amounts of these foods; the advised daily intake for children ages 0.5 to 3 years in the Netherlands was approximately 150 g of fruits, 100 g of vegetables, 70–105 g of bread, and 50–60 g of meat or fish (17). Solid foods were recorded semiquantitatively in the following categories: never, sometimes (1–2 times per week), regularly (3–5 times per week), and frequently (6–7 times per week) (13). The intake was defined as adequate if it was equal to or exceeded the advised daily intake for at least 3 days/week.

The parents were asked to fill in a questionnaire concerning demographic data, parental education, and day care attendance of their child at the time of the interview. When both parents were born in a Western country (Europe, the United States, and Oceania), children were classified as "Western." Educational level of the parents was classified as "low" when they attended primary education, and "intermediate" or "high" when at least 1 of them completed intermediate or higher vocational education/university, respectively. Birth weight, GA, and maternal factors such as (pregnancy-induced) diabetes, hypertension, smoking habits, and the use of iron supplementation were recorded. The mothers of the participating children were asked to give written informed consent for access to their own medical records to verify this information. The SES was determined by using the participants' postal codes. The SES scores are available for each of the 3876 four-digit postal code areas in the Netherlands for 2010. The SES scores are provided by the Netherlands Institute for Social Research and based on the following items: mean annual income per household, the percentage of households with a low income, and the percentage of households with a low level of education. The SES was expressed as a score (range −2.95 to 5.24) with a higher SES score, representing a lower SES (18). Length was measured to the nearest millimeter by using a stadiometer or a length board in children who were not able to stand, and weight was measured to the nearest 0.1 kg by using a digital scale. The length, weight, and body mass index (BMI) were expressed as standard deviation scores (SDS) (19).

Study Parameters and Biochemical Analysis

The primary study parameters were ferritin and Hb. Hb and MCV were performed using Sysmex XE-2100 or XE 5000 (Sysmex Corporation, Kobe, Japan) automated hematology analyzers. CRP was measured using the Unicel DxC 800 clinical chemistry analyzer (Beckman Coulter, Fullerton, CA) or Modular P (F. Hoffmann-La Roche Ltd, Basel, Switzerland). Ferritin concentrations were determined using a Unicel DxI 800 immunochemistry analyzer (Beckman Coulter).

Statistical Analysis

The sample size was based on the prevalence of ID in other European countries (7.2%) (16), and an interim analysis was proposed after half of the children were included. Using these data in a power analysis, it was suggested that a number of 800 children would be sufficient to have 95% confidence limits of ±2%. The results of the planned interim analysis conducted after the inclusion of 400 children showed a 2.5 times higher prevalence of ID than expected and, therefore, we reached sufficient power to answer the study's aim. SPSS (version 18.0; SPSS Inc, Chicago, IL) was used for the statistical analysis. Before analysis, data were checked on normality using histograms and the Kolmogorov-Smirnov test. The univariate analysis was performed using the Student *t* test for continuous variables and the χ^2 test for dichotomous variables, for comparison of means between groups.

Multiple logistic regression analysis with a backward Wald method was used to analyze risk factors for ID with ID as a dependent variable, and perinatal factors (smoking, hypertension, diabetes, the use of iron supplementation during pregnancy, birth weight, and GA), demographic characteristics (age, sex, ethnicity, SES, and day care), and dietary factors (breast-feeding; present use of formula; age at start formula and cow's milk; intake of >400 mL of cow's milk; and adequate intake of fruits, vegetables, bread, and meat) as independent variables. Demographic characteristics and dietary factors with $P \leq 0.05$ in the multiple linear regression analysis were combined in a final multiple logistic regression analysis using a backward Wald method. Statistical significance was defined as $P < 0.05$.

RESULTS

Of the 743 children meeting the inclusion criteria, 527 parents gave written informed consent to participate in the study (70.9%). The resistance against blood drawing was the main reason for parents not to allow their child to participate. In 127 children, it was not possible to obtain blood from the peripheral venous catheter or the blood volume obtained was insufficient to determine the iron status. Of the remaining 400 children (248 children from the

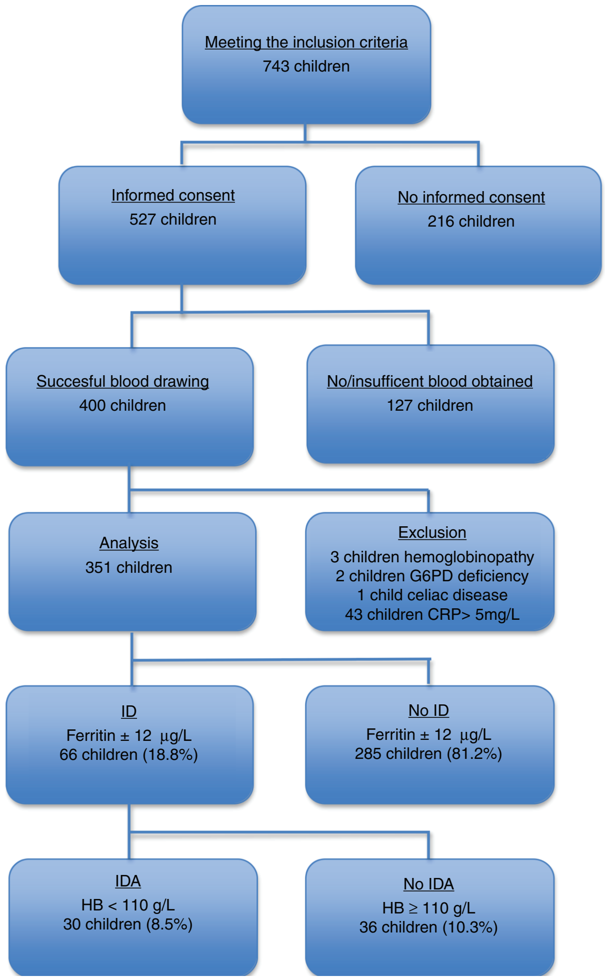

FIGURE 1. Flowchart. CRP = C-reactive protein; G6PD = glucose-6-phosphate dehydrogenase deficiency; HB = hemoglobin; ID = iron deficiency.

Juliana Children's Hospital, 152 children from the Sophia Children's Hospital), 6 children with underlying causes for anemia and 43 children with elevated CRP levels (>5 mg/L) were excluded (Fig. 1). The study included significantly more boys than girls (Table 1) because of the types of surgical interventions, such as correction of hypospadia or orchidopexy, that are carried out most often in healthy children at this age. Mean birth weight and GA were 3366 g (586 standard deviation [SD]) and 39.4 weeks (1.5 SD), respectively. The mean SES was 0.2 (1.5 SD, range −3.0–5.2), and a high educational level was reported in 39.3% and 36.8% of the mothers and fathers, respectively. In our study population 69.2% of the children were classified as Western (Table 1).

Prevalence of ID and IDA

The median values (range) of ferritin, Hb, and MCV, stratified by age are shown in Table 2. ID and IDA were found in 66 (18.8%) and 30 (8.5%), respectively (Fig. 1). The prevalence of ID and IDA was 6.7%, 22.8%, and 25.5%, and 4.8%, 11.0%, and 9.1% in children younger than 1 year, 1 year, and 2 years, respectively.

Risk Factors for ID

Demographic Factors and Anthropometric Measures

We found a similar sex distribution in the ID and the non-ID groups (Table 1). The children with ID were significantly older than children with no ID (Table 1). The visit of preschool/day care was reported less frequently in children with ID compared with those who were without ID (Table 1). No significant differences were found for ethnicity, BMI, SES score (Table 1), parental educational level, and parental age (data not shown).

Perinatal Factors Associated With Iron Status at Birth

The occurrence of maternal smoking, hypertension, diabetes, or the use of iron supplementation during pregnancy was reported in similar rates for both the ID and the non-ID group (data not shown). The mean birth weight did not differ between the ID group and the

TABLE 1. Characteristics of participating children ages 0.5 to 3 years and their parents that may influence iron status

	Total, n = 351	ID, n = 66	No ID, n = 285	*P*
Demographics				
Sex, male$^+$	251 (71.5)	51 (77.3)	200 (70.2)	0.25
Age*, mo	**18.1 (±8.8)**	**21.4 (±8.0)**	**17.4 (±8.8)**	**0.001**
Ethnicity, Western$^+$	243 (69.2)	42 (63.6)	201 (70.5)	0.27
SES*	0.2 (±1.5)	0.2 (±1.5)	0.2 (±1.5)	0.98
Birth weight, g	3366 (±586)	3248 (±521)	3393 (±597)	0.07
Day care, yes$^+$	**194 (55.3)**	**29 (43.9)**	**165 (57.9)**	**0.05**
BMI* (SDS)	−0.1 (±1.3)	−0.1 (±1.2)	−0.1 (±1.3)	0.97
Dietary factors				
Duration of breast-feeding*, mo	**4.0 (±3.9)**	**5.1 (±4.6)**	**3.7 (±3.6)**	**0.03**
Present use of formula$^+$	**184 (52.4)**	**17 (25.8)**	**167 (58.6)**	**<0.001**
Age at start of cow's milk*, mo	**9.5 (±3.7)**	**10.5 (±4.0)**	**9.2 (±3.6)**	**0.03**
Intake of >400 mL cow's milk/day$^+$	**64 (18.2)**	**23 (34.8)**	**41 (14.4)**	**0.00**

Data are presented as $^+$number (%) or *mean (standard deviation). Significant differences between the ID and no ID group are presented in bold. BMI = body mass index; ID = iron deficiency; SDS = standard deviation score; SES = socioeconomical status.

TABLE 2. Indicators of iron status, stratified by age

	0.5–1 y, 105 children	1–2 y, 136 children	2–3 y, 110 children
Ferritin, μg/L	21.6 (7.9–109.6)	18.7 (3.9–55.2)	16.8 (4.6–106.5)
Hb, g/L	108 (81–142)	111 (81–137)	114 (81–134)
Hb, mmol/L	6.7 (5.0–8.8)	6.9 (5.0–8.5)	7.1 (5.0–8.3)
MCV, fL	76 (68–82)	77 (62–85)	78 (66–88)

Median (range) of ferritin, Hb, and MCV. Hb = hemoglobin; MCV = mean corpuscular volume.

non-ID group (Table 1). The prevalence of ID in children with a birth weight <2500 g (3/21 children, 14.3%) and children born <37 weeks' GA (4/22 children, 18.2%) was not significantly different from those with a birth weight >2500 g and born at term ($P = 0.57$ and $P = 0.94$).

Dietary Factors

The present use of breast-feeding and no formula feeding was reported in 6.7%, 2.2%, and 0.9% of children ages 0.5 to 1, 1 to 2, and 2 to 3 years, respectively. The use of breast-feeding in the past was reported in 68.9% of the children. Mean reported duration of breast-feeding was higher in children with ID compared with those who were without ID (Table 1). The formula feeding was introduced after the age of 6 months in 26 children. The prevalence of ID was significantly higher in children who received breast-feeding and no formula feeding before the age of 6 months compared with children in whom formula feeding was introduced before the age of 6 months (45.8% and 16.2%, respectively, $P < 0.001$, odds ratio 3.8, 95% confidence interval 1.6–8.7). The present use of formula, when compared with the use of regular cow's milk, was reported significantly less in children with ID than in those without ID (Table 1). In a subanalysis of 246 children >1 year of age, 92 children (37.4%) received follow-on formula and 12 of these children (13.0%) were iron deficient, whereas among 154 children (62.6%) not receiving follow-on formula, 47 (30.5%) were iron deficient (odds ratio 2.9, 95% confidence interval 1.5–5.9). The intake of >400 mL of cow's milk per day occurred more frequently in children with ID than in those without ID (Table 1), after adjustment for age. There was no difference in the reported intake of meat or other food groups between children with ID or IDA and those without ID or IDA.

The results of a multivariate analysis of dietary factors described in Table 2 showed that the present use of formula was associated with a lower prevalence of ID, whereas intake of >400 mL cow's milk was associated with a higher prevalence of ID, after adjustment for age.

In a final multiple logistic regression analysis of the demographic characteristics and dietary factors that may influence iron status, the visit of preschool/day care, the present use of formula and intake of >400 mL cow's milk remained significantly different between children with ID and those without ID, after adjustment for age (Table 3).

TABLE 3. Multivariate logistic model assessing the relation of ID with the visit of preschool/day care, breast-feeding, duration of breast-feeding, present use of formula, age at start cow's milk, intake of >400 mL cow's milk per day in children ages 0.5 to 3 years

Risk factors for ID	β	95% CI	*P*
Day care, yes^{+}	3.22	1.04–7.19	0.004
Present use of formula, yes^{+}	5.53	1.95–15.60	0.001
Intake of >400 mL cow's milk/day, yes^{+}	2.30	1.04–5.08	0.04

CI = confidence interval; ID = iron deficiency.

DISCUSSION

This study shows that ID and IDA are a common problem in a population of healthy children ages 0.5 to 3 years in the southwestern region of the Netherlands. Our study population was representative of the Dutch population, considering SES with a mean SES score in our population (0.2 [1.5 SD, range −3.0 to 5.2]) that was almost equal to the mean SES score in the general Dutch population (0.00 [1.00 SD, range −3.4 to 5.2]). The reported educational level in our study was representative of the mean educational level in the general Dutch population, with a high educational level reported in 39.3% and 36.8% of the mothers and fathers, respectively, compared with 43% and 35% of the women and men in the general population (20). The ethnicity of our study population was more representative for the multiethnic composition of the population living in the urbanized, southwestern region of the Netherlands (21). The use of formula and present visit of preschool/day care were associated with a lower prevalence of ID, whereas a daily intake of >400 mL of cow's milk was associated with a higher prevalence of ID.

The ID and IDA, as defined according to the present criteria of the WHO (16), were found in 6.7%, 22.8%, and 25.5% and in 4.8%, 11.0%, and 9.1% of the children ages 0.5 to 1, 1 to 2, and 2 to 3 years, respectively. Large variations in the reported prevalence of ID exist in Europe (0%–85%) (8,13,22) and in the United States (7%–21%) (9). In addition, the reported prevalence rates for IDA vary greatly, from <5% in northwest Europe to approximately 50% in some countries in eastern Europe (13,23). These variations are, at least partly, caused by different age groups that have been studied and different criteria that have been used for the definition of ID. There is no agreement on the optimal iron status and the definition of ID in infants and young children. The results of several studies indicated that the thresholds for ferritin as defined by the WHO may be too high (24,25), and, therefore, lower thresholds have been suggested (24,26). Using a lower, more conservative threshold of ferritin <10 μg/L and Hb < 100 g/L in our study (27), ID would be found in 2.9%, 11.8%, and 19.1% and IDA in 0%, 4.4%, and 2.9% of the children ages 0.5 to 1, 1 to 2, and 2 to 3 years, respectively. Another method used to define ID is to use a combination of 2 or 3 abnormal values in a set of multiple iron status indicators (28). There is, however, no consensus about the best combination of indicators to use, and reference ranges for most indicators are poorly defined (24).

The prevalence of ID and IDA may also be influenced by the presence or absence of an infection. Many studies evaluated iron status without the assessment of an acute-phase protein to identify infection (9,13,29). Because most indicators of iron status increase in the presence of infection or inflammation, these data may underestimate the ID prevalence (16). We excluded each child with a CRP ≥ 5 mg/L to rule out any influence of infection. Finally, the variations in ID and IDA prevalence may be caused by demographic and dietary factors that differ greatly between and within countries. In our study we explored the majority of these factors.

In contrast to other studies (5,9,30), we found no influence of ethnicity and SES on the prevalence of ID. In the Netherlands, the mean SES and educational level are high and differences in SES are relatively small. The ethnicity and SES were not associated with differences in dietary patterns in our study, which probably explains the absence of an association between ethnicity or SES and ID in our study.

The introduction of formula after the age of 6 months was associated with a higher prevalence of ID. Similar results have been described in other studies (7,29). Compared to data on the use of breast milk in the Netherlands in 2005 (31), the use of breast-feeding from birth was relatively low in our study (68.9% and 79%, respectively) and formula feeding was introduced before the age of 6 months in a relatively large proportion of the children (92.6%). We suggest that sufficient iron intake from the complementary diet and formula feeding, as an addition to breast-feeding, are the most important factors to prevent ID in children. The studies performed in Iceland (29), Norway (32), and Sweden (33) reported more frequently the use of (follow-on) formula, and thereby less ID than we have found in our study. Moreover, other studies have shown that the use of iron-fortified formula and cereals improve iron intake and iron status in infants (34,35). In this study, the use of follow-on formula was reported in only 55.1% and 15.1% of children ages 1 to 2 and 2 to 3 years, respectively. Therefore, we speculate that the relatively high prevalence of ID and IDA in our study represents insufficient iron intake, as was described in a large food consumption survey in the Netherlands in 2005–2006.

In accordance with other studies (36–38), we found that intake of >400 mL/day cow's milk occurred more frequently in children with ID. Cow's milk has a low iron content. Consuming >400 mL of milk per day is accompanied by less consumption of iron-rich foods and drinks, and these children are more prone to have a poor iron status (39). In our study, a high intake of cow's milk was reported more frequently in children >1 year of age and these children consumed less formula. In a multiple logistic regression analysis, the use of formula was associated with a lower prevalence of ID, whereas the intake of >400 mL of cow's milk was associated with a higher prevalence of ID, after adjustment for age (Table 3).

No difference was observed in the reported consumed amount of meat or iron-containing products other than formula, between children with ID or IDA and those with a normal iron status. A study in 9-month-old infants in Denmark reported similar results (35). We assume that the absence of an association between iron intake and iron status is caused by the variable absorption of iron, depending on the body iron status and diet composition (40). Furthermore, the dietary questionnaire used in this study may be affected by recall bias. The observation that formula was the only iron-containing food group related to iron status underlines its importance in protection against ID. We have found that the prevalence of ID is significantly lower in children who visit preschool/day care than those who stay at home. Similar findings were reported in only 1 other study (9). The attendance of preschool/day care remained significant after the adjustment of parental educational level, SES, and age. The most likely explanation for this observation is that the children who attend preschool/day care centers have a higher iron intake than those who do not. The reported use of formula was, however, lower in children who visit preschool/day care compared with children who stay at home, after adjustment for age (45.1% and 61.5%, respectively, $P < 0.01$). Furthermore, there was no difference in the reported use of breast milk or intake of iron-containing products. Because children visiting preschool/day care spend considerable time under supervision of several different people, assessment of iron intake is likely to be less reliable in these children. We speculate that children eat more and healthier in preschool/day care than parents know because of factors such as using meals collectively with other children, structural moments when meals are used, and more time and attention for eating (41,42).

A limitation of our study is that we cannot completely exclude selection bias because the ethnicity of nonparticipants was not consistently recorded. Because a higher prevalence of ID was reported in ethnic minorities (9), the ethnicity of our population may have influenced the prevalence of ID. We, however, suggest that the influence of selection bias in our study is limited because other demographic characteristics such as sex, age, and SES score were similar in participants and nonparticipants. Moreover, ethnicity of our study population was representative of the southwestern region of the Netherlands.

CONCLUSIONS

In a large study we have shown that the prevalence of ID is high (18.8%) in a well-defined healthy population of 0.5- to 3-year-old children living in the southwestern region of the Netherlands. Visiting preschool/day care and the present use of formula were associated with a lower prevalence of ID, whereas a high intake of cow's milk was associated with a higher prevalence of ID. We actively promote, protect, and support breast-feeding, but for children who are not breast-fed or not fully breast-fed, the use of formula and sufficient iron intake from the complementary diet are the most important factors to prevent ID in them. The protective effect of visiting preschool/day care may be attributed to more intake and healthier dietary habits than at home. More studies are required to disclose in more detail the use of formula and the dietary intake and habits on preschool/day care.

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