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Young children formula consumption and iron deficiency at 24 months in the general population: a national-level study

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Short title: Iron-fortified formula use and iron deficiency

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Abstract (286/300 words)

Background and aims: Iron deficiency (ID) is considered the most frequent micronutrient deficiency in industrialized countries where strategies for its primary prevention vary widely and are insufficiently evaluated. We aimed to study the effectiveness for iron status of a national iron deficiency prevention strategy based on recommendations for young-child formula (YCF) use after age 12 months, taking into consideration other sources of iron and the family's socio-economic status.

Methods: In a cross-sectional observational study conducted in primary care pediatrician offices throughout France from 2016 to 2017, infants aged 24 months were consecutively included for a food survey and blood sampling. Associations between YCF consumption and serum ferritin (SF) level were studied by multivariable regression after adjustment on sociodemographic, perinatal and dietary characteristics, notably other intakes of iron.

Results: Among the 561 infants analyzed, the ID prevalence was 6.6% (37/551; 95% confidence interval [CI] 4.7-9.0). Daily iron intake excluding YCF and total daily iron intake including YCF were below the 5-mg/day recommended average requirements for 63% and 18% of children, respectively. ID frequency was significantly decreased (or SF level was independently higher) with any YCF consumption since age 10 months (odds ratio 0.15, 95% CI 0.07-0.31), current YCF consumption at age 24 months (median SF level 29 vs 21 µg/L if none), prolonged YCF consumption (28 µg/L if > 12 months vs 17 µg/L if none), and increasing daily volume of YCF consumed at age 24 months from a small volume (e.g., 29 µg/L if <100 mL/day vs 21 µg/L if none).

Conclusions: Current or past YCF use was independently associated with a better iron status at age 24 months than non-use. The strategy recommending YCF use at weaning after age 12 months seems effective in the general population.

ClinicalTrials.gov identifier: NCT02484274

Keywords: Iron deficiency; primary prevention; young-child formula; socioeconomic factors, effectiveness; nationwide cohort study

Introduction

Iron deficiency (ID)[1] is considered the most frequent micronutrient deficiency worldwide, including in industrialized countries, and is strongly suspected to be associated with adverse short- and long-term neurocognitive effects when it occurs in neonates and infants [1]. In this context, ID is a target of various primary preventive strategies supported by medical societies and public health authorities, based on advice to parents for consumption of naturally iron-rich foods during complementary feeding, iron fortification (e.g., formula or cereals) or iron supplementation (drops) in their children [2-4]. In some countries like France, the preventive strategy involves both parental education related to complementary feeding and the recommendation for consumption of iron-fortified formulas (IFFs) at breastfeeding cessation [5]. IFFs after age 6 months include "follow-on formulas" and "young-child formulas" (YCFs, sometimes inadequately called "growing-up formula") between age 6 and 10-12 months and after 10-12 months, respectively, to help to ensure the recommended average requirement (AR) of 5 mg/day at this age [5, 6]. The European Food Security and Authority (EFSA) does not recommend YCF as the main source of iron after age 12 months and has criticized YCF-based strategies given the lack of evidence supporting their superiority as compared with balanced diet strategies [7, 8]. In some industrialized countries, balanced diets were recently shown to be rarely achieved at this age at the population level [9, 10].

The efficacy of IFFs has been evaluated by eight clinical trials, seven of which found a statistically significant effect of IFFs use on iron status [11-17]. The efficacy of IFFs seems well established at the scale of randomized trials, but this conclusion cannot be extrapolated to their effectiveness, notably after age 12 months, at the population level. Indeed, the ability of IFF-based strategies to reach disadvantaged families (with low economic and/or education

[1] **Abbreviations:** AR: average requirements; EFSA: European Food and Security Authority; ID: iron deficiency; IFF: iron-fortified formula; SF: serum ferritin; YCF: young children formula.

level) [18-21], who are at greatest risk of ID [2-4, 22], is poorly known and should be evaluated. Moreover, to be reliable, such demonstration must take into consideration between-country and between-region variability in iron intake from non-dairy food. Thus, the evaluation of the effectiveness of IFF-based prevention strategies requires large populations with a diversified recruitment collecting sociodemographic, biological and dietary data. Only three studies with a closely approaching design are available and were performed in Ireland, The Netherlands, and the United Kingdom [23-25]. They all found a protective effect of YCF on iron status at age 12 to 24 months (e.g., adjusted odds ratio [OR] for ID was 5.5 for lack of use of YCF [24]). However, these studies had limitations that prevent definitive conclusions on the effectiveness of YCF-based strategies: selection bias (single-center recruitment [25], children requiring surgery [24]), strong attrition [23, 25], dietary survey not following EFSA recommendations [24], and/or lack of multivariate analyses to take into consideration socio-economic status or non-dairy iron intake [23].

A non-biased evaluation of the independent effect of YCF at the national level is needed to produce evidence to discourage or support YCF-based strategies after age 12 months versus other strategies for ID primary prevention. Here we aimed to evaluate the effectiveness of a strategy for ID prevention based on the recommendation of YCF use after age 12 months at a national level by analyzing its association with iron status in children aged 24 months, taking into account other sources of iron and the family's socio-economic status.

Methods

General methodology

We conducted a cross-sectional observational study in primary care paediatric private practices throughout France from January 2016 to December 2017, named the CARMA study. The signed consent from at least one parent was obtained before inclusion. The study

121 protocol was approved by local ethics and administrative authorities (CPP IDF III no. 3295)
122 and was registered (ClinicalTrials.gov identifier: NCT02484274). We used the Strengthening
123 the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to report this
124 study (**Supplemental Table 1**).
125
126 *Participant selection*
127 Investigators were recruited from the directory of the French Ambulatory Pediatricians
128 Association (the national association of primary care pediatricians, n≈1600). Invitations to
129 participate were sent to all pediatricians. Among the respondents, a selected sample of about
130 120 pediatricians stratified on the 21 French continental regions was recruited to take in
131 consideration the between-region variability. Investigator recruitment was secondarily
132 extended to all members of the association given difficulties in recruiting participants in this
133 complex study. This recruitment in primary care pediatrician offices and different regions of
134 the country aimed at including infants from the general ambulatory population at a national
135 level. Each pediatrician was asked to include 10 consecutive children, aged 22 to 26 months,
136 usually living in France (**Supplemental Figure 1**), who had health insurance coverage, and
137 were not known to be affected by at least one of the following diseases that may affect iron
138 metabolism: transfusion(s) since birth, celiac disease, inflammatory bowel disease, cystic
139 fibrosis, other enteropathy (except allergy to cow's milk protein), enteral nutrition of more
140 than 15 days in the last 6 months, chronic hemolytic diseases, chronic renal failure,
141 hemophilia, hemochromatosis, malignant diseases and lead poisoning.
142
143 *Data collection*
144 The study phases are described in detail in **Supplemental Methods**. In summary, current
145 sociodemographic data, past and current main dietary habits and medical data were collected

146 by the investigator at inclusion. During the month after inclusion, a dietary survey was
147 performed according to the EFSA reference methodology. Parents recorded all ingesta per 24-
148 hr period over three non-consecutive days (two during the week and one during the weekend)
149 by using paper diaries, as in previous studies [26]. Investigators and on-line research
150 assistants helped parents complete the survey when needed. Dietary data from these diaries
151 were double-entered, tested for consistency, and transformed by using the ANSES-Ciqual
152 nutrient composition table for non-infant foods [27] and the infant-specific table designed for
153 the French Children's Food Union [28]. With this process, we obtained the ingesta and their
154 source for each individual and each nutrient.

155 After the dietary survey, a fasting blood sample was taken; serum ferritin (SF) and C-
156 reactive protein (CRP) were measured centrally in a unique laboratory after refrigerated
157 transport of blood samples at +2 to +8°C. SF was measured by immunochemiluminescence
158 (COBAS -Roche Diagnostics- COBAS 6000 E601, measurement range: 0.5-2000 µg/L, intra-
159 and inter-series coefficients of variation <1.1% and <5.7%, respectively) and CRP was
160 measured by immunoturbidimetric assay.

161 In case of fever or any other condition that could alter the ingesta or biological iron
162 status (e.g., bronchiolitis, gastroenteritis), the dietary survey and blood sampling were
163 postponed to 15 days after discontinuation of symptoms. Children for whom no blood sample
164 was taken, whose parents did not complete the dietary survey, or with a CRP level ≥10 mg/L
165 were excluded from the statistical analyses.

166

167 *Statistical analyses*

168 We first described the general characteristics of the studied and analyzed population and
169 compared them to those of the 2016 French National Perinatal Survey, a national
170 representative sample of births (n=13 148) [29]. Second, we characterized iron intake

specifically and its distribution considering all sources from the whole diet including YCF or excluding YCF. Third, we described the distribution of SF and used multivariable linear regression models (after logarithmic transformation of SF [30]) to study the crude then adjusted association of SF with past dietary habits (including declared YCF consumption) and current ingesta (including declared and measured YCF consumption) and perinatal and sociodemographic characteristics. The specific sources of iron evaluated in the analyses are listed as dietary characteristics in **Table 1**. YCF consumption was defined in several ways: "any consumption after 10 months" and "current consumption at age 24 months" (two binary [no/yes] declarative variables), "daily volume consumed" in five categories (measured variable in the dietary record) to evaluate a “dose effect”, "consumption duration" (declarative variable) used as continuous variable, then in three categories to evaluate a “time effect”. We evaluated the duration of consumption of any IFF since age 6 months by a continuous variable corresponding to the sum of consumption duration for both follow-on formula and YCF. This variable represented the cumulative iron intake from dairy food at about age 6 months. The statistical handling of other variables is detailed in **Supplemental Methods**. Finally, SF was dichotomized with a 12-µg/l threshold to define ID, as suggested [2, 4, 31]. The prevalence of ID and its crude associations with potential determinants were studied by univariate analysis. No multivariable analysis was used given the low number of ID cases.

No multi-level model was used in these analyses despite recruitment in different practices because the variance of a multilevel model with random intercept including only the center of recruitment was low, 7%. For all continuous variables, the lack of deviance to linearity was searched and a fractional polynomial of degree 2 at most was used if appropriate. Several sensitivity analyses were performed by repeating the univariate analyses with a 10-µg/l threshold of SF to define ID [2, 4, 32], repeating regressions analyses without sociodemographic characteristics or studying specific associations of perinatal and

196 sociodemographic variables with iron status. Missing data (≤2%) were not imputed. The
197 number of participants required (n=1000) was calculated with a very conservative hypothesis
198 (**Supplemental Methods**); the recruitment was stopped prematurely for financial reasons.
199 The analyses involved use of Stata/SE v13.1 (StataCorp, College Station, TX, USA).
200

201 **Results**

202 *Participants*

203 A total of 830 young children were included by 58 pediatricians from 16 French regions; 15
204 were excluded because of non-eligibility criteria, 212 (26%) because of no blood sample, 8
205 (1%) because of lack of dietary survey, 31 (5%) because of CRP level ≥10 mg/L, and 3
206 (0.5%) because of missing data for SF level (**Supplemental Figures 1 and 2**), leading to an
207 analyzed population of 561 infants. The analyzed population was less disadvantaged than the
208 2016 French National Perinatal Survey population but did not differ from the non-analyzed
209 population (**Supplemental Table 2**).

210 In the analyzed population, the mean age of children was 24 months (SD 0.6), 49%
211 were girls, 3.6% had cow's milk protein allergy, and 10% had received iron supplementation
212 according to parents. YCF was currently used in 73% of the population (408/561, 95%
213 confidence interval [CI] 69-76) and cow's milk in 33% (186/561, 95% CI 29-37). The mean
214 and median total iron intake for the population was 8.2 mg/day (95% CI 7.8-8.6) and 7.6
215 mg/day (interquartile range [IQR] 5.6-9.8). The mean iron intake for the population from all
216 food excluding YCF and from YCF only was 4.7 mg/day (95% CI 4.6-4.9) and 3.5 mg/day
217 (95% CI 3.1-3.8). The median iron intake for the population from all food excluding YCF and
218 from YCF only was 4.3 mg/day (IQR 3.4-5.7) and 3.1 mg/day (IQR 0-5.2). Daily iron intake
219 for the population from all food excluding YCF and total daily iron intake including YCF was

below the 5 mg/day AR for 63% (95% CI 59-67) and 18% (95% CI 15-22) of children (**Figure 1**).

Median SF was 26 µg/L (IQR: 20-37, mean: 31 [SD 21]) (**Supplemental Figure 3**). After dichotomization of SF at thresholds <12 and <10 µg/L, ID prevalence was 6.6% (37/561, 95% CI 4.7-9.0) and 3.9% (22/561, 95% CI 2.5-5.9) (**Table 1** and **Supplemental Table 3**).

Dietary factors associated with iron status

On univariate analysis, SF was significantly ($p < 0.05$) lower with cow's milk use beginning before age 24 months (median 23 vs 28 µg/L if not) or its current use at 24 months (23 vs 28 µg/L if not) and with increased iron intake from all food excluding YCF (β coefficient = -0.03, 95% CI -0.05-[-0.01]) (**Table 1**). We found no significant association between SF and exclusive breastfeeding beyond 6 months or cow's milk consumption duration (**Table 1**). SF was significantly higher with follow-on formula use between age 6 and 12 months (27 vs 23 µg/l if not), YCF use since age 10 months (27 vs 17 µg/L if not) or current use at 24 months (29 vs 21 µg/L if not), daily volume of YCF consumed (29 µg/L if <100 mL/day vs 21 µg/L if none), increasing YCF consumption duration (28 if > 12 months vs 17 µg/L with no YCF), and increasing IFFs consumption duration (β coefficient = 0.05, 95% CI : 0.03-0.07; i.e., 28 if > 12 months vs 17 µg/L if no IFF, this last result is not shown in Table 1) (**Table 1**). For the 58 children with a high daily volume of YCF consumed (≥450 mL; i.e., the 90th percentile), we found no significant increase in mean SF level (34 vs 31 µmol/L with daily YCF volume <450 mL, p=0.23) or median SF level [90th percentile] (26 [51] vs 27 µmol/L [58] with daily YCF <450 mL).

In several multivariable linear models adjusting for co-variables of interest (**Table 2**) and after checking for no significant collinearity between YCF and cow's milk consumption,

245 SF was positively associated with YCF consumption, whether described by a binary variable
246 (any use after age 10 months), volume consumed or duration of consumption. SF was also
247 associated with duration of IFFs consumption since age 6 months (**Table 2**). In all
248 multivariable models, unfavorable iron status was associated with a medical history of
249 prematurity, an elevated rank among siblings and disadvantaged social situation: low father's
250 education level (**Table 2, Supplemental Table 6**) as in univariate analyses (**Supplemental**
251 **Tables 4 and 5**).

252 After dichotomizing SF at the 12-µg/L threshold, ID was significantly associated
253 ($p < 0.05$) with the same markers as SF used as a continuous variable (**Table 1**) except iron
254 intake from all food excluding YCF. For example, ID was significantly decreased with YCF
255 use since age 10 months (25% vs 5% with YCF use, OR 0.15, 95% CI 0.07-0.31).

256 Sensitivity analyses at the 10-µg/L threshold found a statistically significant
257 association between ID ($p < 0.05$) and the same variables as with the 12-µg/L threshold,
258 except for infant formula use, which was significant at the 10-µg/L threshold only
259 (**Supplemental Table 3**). Similar results were found in the sensitivity analyses for the
260 multivariate models without adjustment for sociodemographic variables comparatively to
261 those adjusted for sociodemographic variables (**Supplemental Table 6**).

262

263 **Discussion**

264 *Main results*

265 With a simultaneous collection of medical, biological and dietary data at the national scale, a
266 design rarely achieved in the literature [23, 24], we found a protective role of YCF use on ID
267 in children at age two years in the general population. This protective role was strong with,
268 for example, a reduction of one-fifth of ID with YCF use since age 10 months (OR 0.15, 95%
269 CI 0.07-0.31). This protective role was consistent according to the different definitions of

YCF consumption (amount, duration), measured either retrospectively by asking parents about the past consumption or prospectively by quantifying current consumption with a dietary survey. This protective role is consistent with results from clinical trials [11-17] and previous observational studies [23-25, 33] and was independent of potential confounders such as disadvantaged social situation, non-dairy iron intake and iron supplementation, which were not always taken into account in previous studies [23, 24]. This protective role is easy to conceive theoretically because iron given to young children in any form is supposed to increase their iron stores in the absence of concurrent loss or illness, given the almost closed-circuit metabolism of iron [4, 31, 34, 35].

Our study provides information on how YCF-based strategies could help improve iron status in the general population. First, the mean total iron intake was 8.2 mg/day, higher than the 5 mg/day AR recommended in Europe by the EFSA, in 82% of children [6]. The mean intake from all sources excluding YCF was 4.7 mg/day and from YCF only was 3.5 mg/day for the population analyzed. Added to the EFSA recommended strategy based on naturally iron-rich food, YCF use allowed for a reduction from 63% to 18% of children with below the 5-mg/day AR. Thus, YCF use added to the rest of the diet allowed 45% of children to reach the daily AR. Furthermore, the YCF impact on iron status was detectable even for a small daily volume consumed, but the increase >500 mL/day was not associated with a significant increase in SF. Results from several studies support that a small volume of YCF (100–300 mL/day) allows for reaching the recommended AR [36-38]. Iron bioavailability mechanisms are complex, and the amount of iron ingested is not equal to the amount of iron absorbed. This absorption depends notably on the origin of iron (haem or not), the type of other concomitant ingested food and the period of life, notably acceleration of growth [2-4, 31, 39]. Thus, even a small amount of iron with IFFs could improve iron status [40, 41].

294 Second, another finding helps in understanding how YCF use could help improve iron
295 status: the association observed between increased SF and consumption duration of IFFs since
296 age 6 months (i.e., follow-on formula, then YCF). This "time effect" implying the duration of
297 exposure to IFFs suggests a role of long-term, "cumulative", consumption of IFFs in iron
298 status at age 24 months. This finding, as the previous one about a non-linear effect of YCF
299 volume consumed on iron status, can probably be explained in part by the role of hepcidin in
300 regulating iron absorption and the prevention of iron overload if iron reserves are already
301 high. Indeed, this peptide synthetized by hepatocytes participates in regulating iron absorption
302 by enterocytes: when iron reserves are high, hepcidin synthesis increases and induces the
303 degradation of ferroportin on enterocytes and macrophage membranes, thus limiting iron
304 release in blood circulation [35, 39, 42], whereas when iron reserves are low, hepcidin
305 synthesis is downregulated, thereby increasing iron bioavailability. The potential risk of iron
306 excess with fortification use can be raised. Use of IFFs has been found associated with iron
307 intake above the tolerable upper intake level but not excess iron stores based on SF
308 distribution in infants [38, 43]. In our analyzed population, we found no significant difference
309 in SF distribution with high daily volume consumed. This study suggests that small amounts
310 of iron ingested regularly over time could be more beneficial to prevent ID than high amounts
311 over a short period without leading to iron excess stores.

312 In this study, we found other determinants of iron status at 24 months usually
313 identified in the literature: medical history of prematurity and factors linked to deprived
314 situation (low father's education level) or family situation (high rank in siblings). The
315 independent association found between iron status and a history of prematurity, remaining
316 even after taking into account iron supplementation, suggests that this sub-population at high
317 risk of ID should benefit from more specific prevention and monitoring of iron status, as
318 previously found [44, 45]. "Exclusive" breastfeeding beyond 6 months is a classical risk

319 factor for ID [46], but it was not independently associated with iron status in our study,
320 probably because assessment of iron status occurred late, at 24 months, and many other
321 nutritional factors may have intervened between 7 and 24 months.
322
323 *Strengths and limitations*
324 Our study has several strengths. The measurements of iron biomarkers were standardized and
325 centralized as recommended by the World Health Organization [47], as was the evaluation of
326 nutritional intake with a dietary survey performed on three non-consecutive days to improve
327 the accuracy of intra-individual variability, as recommended by the EFSA [26]. Biological
328 and dietary data were measured independently, with blinding. A specific strength of this study
329 is the consideration of all sources of iron besides YCF in multivariate analyses in contrast to
330 some other national studies [23, 24].
331 There were several limitations. First, the analyzed population presented a selection
332 bias as shown by less frequent disadvantaged situations than in all births. This bias can be
333 explained mainly by recruitment by pediatricians and the significant attrition due notably to
334 failure to obtain a blood sample (32% of the studied population). Indeed, only 20% of French
335 children at age 24 months are followed by a pediatrician [48] and those who accepted to
336 participate in this complex study were probably familiar with clinical research. The study
337 possibly selected families interested in the topic of nutrition with good knowledge and
338 practices regarding ID prevention. This selection bias probably led to underestimating the ID
339 prevalence, which was regardless close to the most recent national estimations [49].
340 Furthermore, this potential bias could not have altered the associations between iron status
341 and YCF consumption in the analyzed children. Second, the recruitment was stopped before
342 the calculated sample size was achieved, and the attrition may have led to loss of statistical
343 power. However, the sample size was calculated on the basis of a very conservative

hypotheses on expected associations that were not confirmed by the study (associations were much stronger than expected). To manage the lack of power, the main analyses were finally based on ID defined by SF level as a continuous variable. Finally, as in other studies, some inaccuracies may have occurred during the declarative food intake data collected by the pediatrician and regarding the quantities assessed by the parents during the survey. However, they may have been limited by the checks of a well-trained dietician as detailed in **Supplemental Methods**. Besides, these inaccuracies occurred with blinding to iron status, so they may have led to only a non-differential bias and a loss of statistical power.

Implications

In this first national-level study taking into account non-dairy iron intake and iron supplementation and the family's socio-economic status, YCF consumption allowed for reaching the required iron AR in 45% of children who were not reaching it otherwise by dietary intake. YCF use was strongly and independently associated with better iron status than non-use. The biological benefit of YCF was obtained even for a limited daily amount, about 200 mL/day, especially when implemented over a long period. These findings support national strategies for ID prevention based on the recommendation for YCF consumption after age 12 months [7, 8]. YCF consumption seems a simple way to supply young children with the recommended iron intake and reach the recommended AR added to the rest of the diet in practice, according to the family's and country's culture. Indeed, a well-balanced diet by solid food is possibly difficult to achieve at this age [9, 10]. These findings should trigger measures to enhance YCF accessibility to at-risk families (i.e., those in disadvantaged situations).

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Conflict of interest statement:

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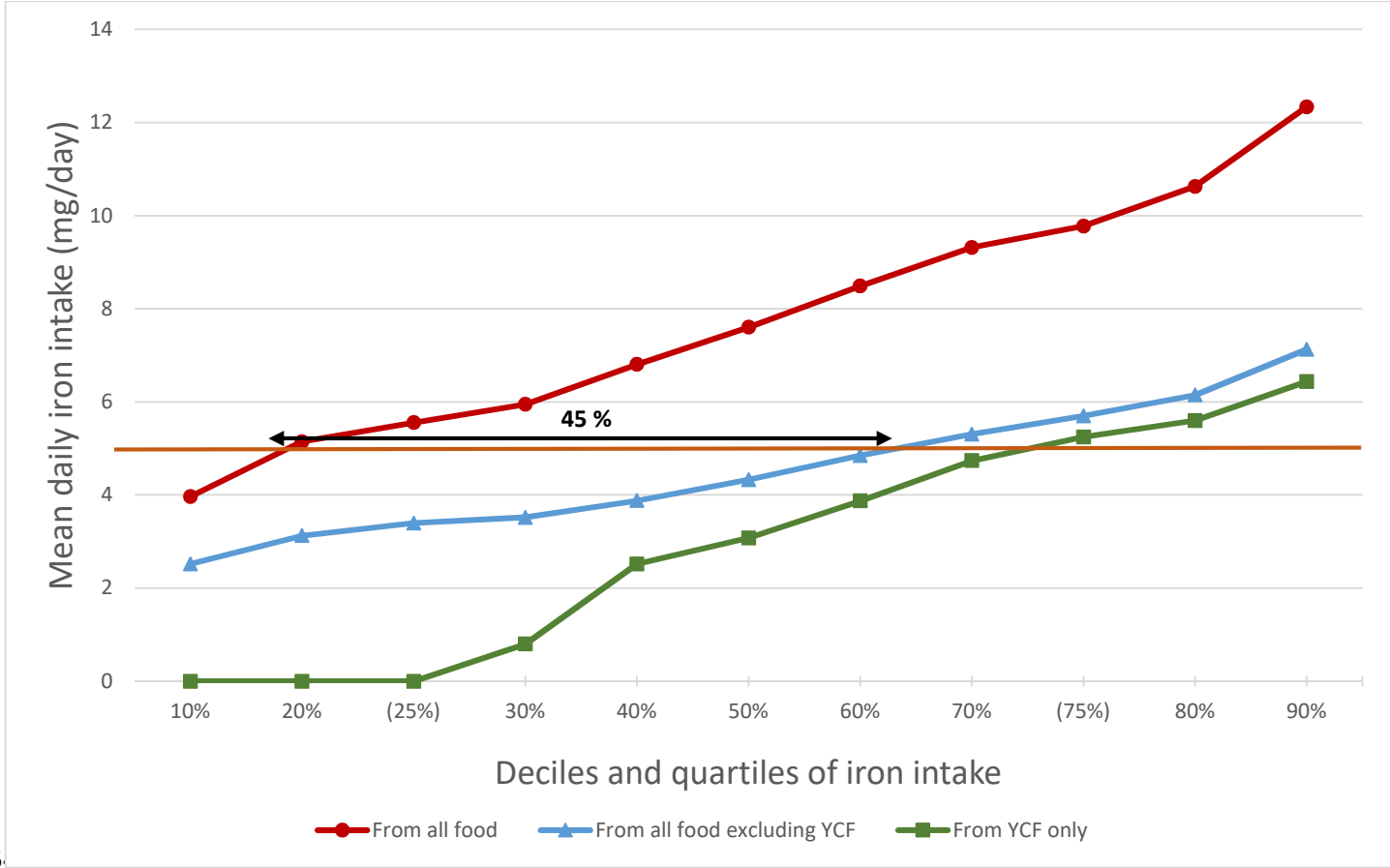

Figure 1. Distribution of mean daily iron intake (mg/day) according to deciles and quartiles of iron intake stratified by iron sources (n=561): from all food (red line), from all food excluding young-child formula (YCF, blue line), and YCF only (green line).

Deciles and quartiles were calculated separately by iron sources. At a consequence, for each decile or quantile, mean daily iron intake from all food is not equal to the addition of mean daily iron intake from all food excluding YCF + YCF only.

In children who did not reached the required iron average requirements recommended from all food without YCF, 45% reached this threshold if iron intake from YCF was considered.

Horizontal orange line: threshold of iron intake of 5 mg/day corresponding to the average requirements recommended by the European Food Security and Authority (EFSA) at age 24 months [6]

558 **Table 1.** Dietary characteristics of children and univariate associations with serum ferritin
559 level and iron deficiency (ID) at a threshold of 12 µg/L (by milk according to the age of
560 consumption)

561

Characteristics	n (%)[a]	Serum ferritin level (µg/L)			ID, serum ferritin level < 12 µg/L			
		Median[b]	IQR[b]	p[c]	ID[a] (%)	No ID[a] (%)	OR[d]	95% CI [e]
	n = 561				n = 37	n = 524		
"Exclusive" breastfeeding > 6 months								
No	484 (86)	27	20-37	-	5	95	-	-
Yes	77 (14)	26	17-35	0.07	16	84	3.39	1.62-7.07
Infant formula: consumption 0 to 6 months								
No	128 (23)	26	19-35	-	10	90	-	
Yes	433 (77)	27	20-37	0.11	6	94	0.52	0.26-1.05
Late food diversification > 6 months								
No	546 (98)	26	20-37	-	7	93	-	-
Yes	10 (2)	30	23-38	0.83	10	90	1.57	0.19-12.77
Follow-on formula: consumption 6 to 10-12 months								
No	68 (12)	23	15-35	-	21	79	-	-
Yes	492 (88)	27	20-37	<0.01	5	95	0.19	0.09-0.39
Follow-on formula: consumption duration (months) [f]								
	5.7 (1.5)	0.01	-0.03-0.04	0.65	5.8 (1.7)	5.7 (1.4)	1.05	0.80-1.37
YCF: consumption after 10 months								
No	48 (9)	17	11-30	-	25	75	-	-
Yes	512 (91)	27	21-37	<0.001	5	95	0.15	0.07-0.31
YCF: current consumption at 24 months								
No	153 (27)	21	14-29	-	18	82	-	-
Yes	408 (73)	29	22-40	<0.001	2	98	0.10	0.05-0.22
Current YCF: daily volume consumed								
No consumption	150 (27)	21	14-30	-	18	82	-	-
< 100 mL / day	175 (31)	29	22-43	<0.001	1	99	0.05	0.01-0.23
100-300 mL/ day	103 (18)	28	21-35	<0.001	7	93	0.33	0.14-0.80
300-500 mL / day	101 (18)	30	21-40	<0.001	1	99	0.05	0.01-0.34
≥ 500 mL / day	32 (6)	27	22-42	<0.001	0	100	0.14	0.01-0.91
YCF: consumption duration (months) [f]								
	11.3 (3.0)	0.04	0.02-0.05	<0.001	8.5 (4.7)	11.4 (2.9)	0.82	0.74-0.90
YCF: consumption duration								
No consumption	48 (9)	17	11-30	-	27	73	-	-
≤ 6 months	61 (11)	21	14-34	0.09	15	85	0.47	0.18-1.21
> 6 and ≤ 12 months	235 (44)	27	21-36	<0.001	3	97	0.08	0.03-0.22
> 12 months	197 (36)	28	21-41	<0.001	3	97	0.08	0.03-0.24
IFFs: consumption (since age 6 months) duration (months) [f]								
	15.3 (5.3)	0.05	0.03-0.07	<0.001	8.9 (7.3)	15.8 (4.8)	0.85	0.81-0.89
Cow's milk: consumption beginning before 24 months								
No	356 (64)	28	21-40	-	3	97	-	-
Yes	201 (36)	23	15-34	<0.001	13	87	5.98	2.75-13.00
Cow's milk: current consumption at 24 months								
No	375 (67)	28	21-39	-	3	97	-	-
Yes	186 (33)	23	16-35	<0.001	14	86	5.38	2.59-11.15
Cow's milk: consumption duration (months) [f]								
	7.4 (4.4)	-0.01	-0.04-0.01	0.15	9.4 (4.7)	7.1 (4.3)	1.13	1.02-1.25
Dietary iron intake from all food excluding YCF [f] (mg/day)								
	4.7 (2.2)	-0.03	-0.05-(-0.01)	0.01	5.2 (2.8)	4.7 (2.2)	1.10	0.96-1.25
Iron supplementation since birth [g]								
No	503 (90)	26	20-36	-	7	93	-	-
Yes	57 (10)	29	22-41	0.17	4	96	0.49	0.11-2.08

562
563 [a] or mean (SD) if the "characteristics" variable is continuous
564 [b] or β coefficient of a simple linear regression after logarithmic transformation (instead of medians) and 95% confidence interval (CI,
565 instead of interquartile range [IQR]) if the « characteristics » variable is continuous
566 [c] Degree of significance of the Student test, Kruskal-Wallis test or of the β coefficient of a simple linear regression (univariable analyses
567 after a logarithmic transformation of the dependent variable: serum ferritin level)
568 [d] For cells with a zero value, 1 was added to all values of the contingency table as suggested [50]
569 [e] 95% CI of odds ratio (OR) in multivariable analyses
570 [f] no deviance to linearity in the linear model or the univariate logistic regression model
571 [g] no change in the results taking into account time interval between iron supplementation and serum ferritin level measure
572
573 Abbreviations: IFF = iron fortified formula, YCF = young-child formula
574

575 **Table 2.** Adjusted analyses of associations between serum ferritin level and young-child
576 formula (YCF) consumption, other dietary, perinatal and sociodemographic characteristics

577

Characteristics	n (%)[a]	Serum ferritin level (µg/L)							
	n = 561	β[b]	95% CI [f]	β[c]	95% CI [f]	β[d]	95% CI [f]	β[e]	95% CI [f]
YCF considering different definitions									
Consumption of YCF after 10 months									
No	48 (9)	-	-	-	-	-	-	-	-
Yes	512 (91)	0.28	0.12-0.45	-	-	-	-	-	-
Daily volume of YCF consumed (mL/day)									
No YCF	150 (27)	-	-	-	-	-	-	-	-
< 100	175 (31)	-	-	0.34	0.20-0.47	-	-	-	-
100-300	103 (18)	-	-	0.25	0.10-0.39	-	-	-	-
300-500	101 (18)	-	-	0.33	0.18-0.48	-	-	-	-
≥ 500	32 (6)	-	-	0.39	0.17-0.60	-	-	-	-
YCF consumption duration (months) [g]									
	11.3 (3.0)	-	-	-	-	0.03	0.01-0.04	-	-
Duration of consumption of IFFs (since age 6 months) [g]									
	15.3 (5.3)	-	-	-	-	-	-	0.03	0.01-0.06
Other dietary characteristics									
« Exclusive » breastfeeding > 6 months									
No	484 (86)	-	-	-	-	-	-	-	-
Yes	77 (14)	-0.08	-0.21-0.06	-0.12	-0.24-0.02	0.04	-0.11-0.18	0.06	-0.08-0.21
Late food diversification > 6 months									
No	546 (98)	-	-	-	-	-	-	-	-
Yes	10 (2)	0.13	-0.21-0.46	0.13	-0.20-0.46	0.07	-0.31-0.45	0.14	-0.18-0.47
Cow's milk consumption beginning before 24 months									
No	356 (64)	-	-	-	-	-	-	-	-
Yes	201 (36)	-0.17	-0.26-(-0.07)	-0.05	-0.16-0.07	-0.12	-0.23-(-0.01)	-0.12	-0.22-0.01
Dietary iron intake from all food excluding YCF [h] **(mg/day)**									
Continuous	4.7 (2.2)								
< 3.5	161 (29)	-	-	-	-	-	-	-	-
3.5–7	337 (60)	*-0.05* [h]	*-0.21-0.12*	*-0.06* [h]	*-0.22-0.11*	-0.06	-0.17-0.04	-0.06	-0.16-0.04
7–10.5	48 (9)	*-0.10* [h]	*-0.29-0.10*	*-0.11* [h]	*-0.30-0.09*	-0.01	-0.19-0.17	-0.02	-0.19-0.15
≥ 10.5	15 (3)	*-0.12* [h]	*-0.32-0.09*	*-0.13* [h]	*-0.33-0.07*	-0.17	-0.51-0.16	-0.16	-0.46-0.14
Iron supplementation since birth [i]									
No	503 (90)	-	-	-	-	-	-	-	-
Yes	57 (10)	0.13	-0.03-0.29	0.14	-0.02-0.29	0.13	-0.03-0.29	0.14	-0.02-0.30

578
579 [a] or mean (SD) if the "characteristics" variable is continuous
580 All the following multivariable linear models were adjusted on YCF consumption (considering different methods of coding, cf. notes below),
581 exclusive breastfeeding > 6 months, late food diversification > 6 months, cow's milk consumption, dietary iron intake excluding YCF, iron
582 supplementation, sex, prematurity, birth weight < 2500 g, rank in siblings, country of birth, education level, and unemployment of parents,
583 family having a health coverage fully funded publicly. The dependent variable "serum ferritin level" underwent a logarithmic transformation.
584 [b] β coefficient of a multiple linear regression model using the binary variable YCF formula consumption (no/yes)
585 [c] β coefficient of a multiple linear regression model using the variable daily volume of YCF consumed
586 [d] β coefficient of a multiple linear regression model using the variable duration of consumption of YCF only
587 [e] β coefficient of a multiple linear regression model using the variable duration of consumption of iron-fortified formula since 6 months-old
588 [f] 95% CI of the β coefficient of a multiple linear regression model corresponding
589 [g] no deviance to linearity
590 [h] creation of a fractional polynomial degree 2 for this variable in a few models because of deviance to linearity (as shown by italics). Results
591 for dietary iron intake excluding YCF are presented by categories for ease of reading
592 [i] no change in the results taking into account time interval between iron supplementation and serum ferritin level measure
593
594 Perinatal and sociodemographic variables in these models are not shown: in all models a lower SF was independently associated with a
595 medical history of prematurity, a high rank in siblings, and a low father's education level
596
597 Abbreviations: CI = confidence interval, IFF = iron fortified formula

598
599