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Modeled healthy eating patterns are largely constrained by currently estimated requirements for bioavailable iron and zinc – a diet optimization study in French Adults.

**Alison Dussiot¹, H  l  ne Fouillet¹, Juhui Wang¹, Marion Salom  ¹, Jean-Fran  ois Huneau¹,
Emmanuelle Kesse-Guyot², Fran  ois Mariotti¹**

¹ Universit   Paris-Saclay, AgroParisTech, INRAE, UMR PNCA, 75005, Paris, France

² Sorbonne Paris Nord University, Inserm, INRAE, Cnam, Nutritional Epidemiology Research Team (EREN),
Epidemiology and Statistics Research Center – University of Paris (CRESS), 93017, Bobigny, France

Corresponding author: Professor Fran  ois Mariotti, 16 rue Claude Bernard, 75005 Paris, France,
francois.mariotti@agroparistech.fr

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Conflict of Interest

None.

List of abbreviations

ANSES, French Agency for Food, Environmental and Occupational Health & Safety;

DALYs, Disability Adjusted Life Years;

FBDG, Food-based dietary guidelines;

Flex, Flexible model;

NFlex, Non-Flexible model

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

Abstract

1 Background: Healthier dietary patterns involve more plant-based foods than current Western diets rich in
2 animal products containing high levels of bioavailable iron and zinc. Little consideration is given to the
3 bioavailability of iron and zinc when studying healthy eating patterns.

4 Objectives: Our aim was to determine whether currently estimated requirements for bioavailable iron and
5 zinc limit the identification of healthier dietary patterns.

6 Methods: Using dietary data from a representative French survey and multi-criteria non-linear
7 optimization, we identified diets that maximize health criteria based on Food-Based Dietary Guidelines
8 and concomitantly depart only minimally from the observed diet, while complying with all nutrient
9 reference values either strictly (non-flexible optimization) or by allowing bioavailable iron and zinc below
10 the current reference values, but to a limited extent (flexible optimization). Using a comparative risk
11 assessment model, we estimated the resulting impact on cardiometabolic and colorectal cancer
12 mortality/morbidity, and changes to iron-deficiency anemia.

13 Results: Under non-flexible optimization, reference values for bioavailable iron and zinc were the most
14 binding of the 35 nutrient constraints and modeled diets displayed considerable redistributions within
15 grains and meat. With flexible optimization, modeled diets were healthier as they contained less red meat
16 and more whole-grain products, but would increase iron-deficiency anemia to 5.0% (95% CI: 3.9%, 6.4%).
17 Globally, in terms of Disability Adjusted Life Years (DALYs), as the loss due to anemia would represent <30%
18 of the gain otherwise made on chronic diseases, adding flexibility in the iron and zinc reference values
19 would result in a further 18% decrease in the disease burden from 84,768 (95% Uncertainty Intervals (UI):
20 81,066, 88,470) to 99,689 (95,787, 103,591) DALYs averted.

21 Conclusions: Currently estimated requirements for bioavailable iron and zinc proved to be critical factors
22 when modelling healthy eating patterns. Considering lower reference values enables the identification of
23 diets that are apparently healthier overall.

24 **Key words:** diet optimization, healthy diet, dietary requirements, dietary patterns, iron and zinc
25 bioavailability

26

27 **Introduction**

28 Nutritional adequacy depends on both the intake of nutrients and their bioavailability, the latter defined
29 as the proportion of the ingested nutrient that is made available for use in normal functions (1). The
30 absorption of non-heme iron and zinc, in particular, can vary as a function of many physiological and
31 dietary factors. Phytate is known to inhibit both the absorption of non-heme iron and zinc (2–4), so that
32 individuals consuming phytate-rich diets, high in plant products, have a greater dietary requirement for
33 iron and zinc (3,5). The intake of many nutrients and their status vary largely as a function of the type of
34 dietary pattern, and Western diets that are more reliant on animal sources, tend towards a better
35 nutritional status regarding iodine, vitamin B12, calcium, iron and zinc (5).

36 However, current western diets are making a major contribution to the burden of disease (6). Healthier
37 dietary patterns have been identified using different approaches, including historical diets such as the
38 Mediterranean diet (7), modeled Healthy Eating Patterns underlying Food-Based Dietary Guidelines
39 (FBDG)(7–9) or prospective scenarios for human and planetary health (10,11). All these diets contain less
40 red and processed meats and more whole grains, pulses, nuts, fruit and vegetables. They would therefore
41 tend to reduce bioavailable iron and zinc by reducing both the intake of zinc and heme iron and the
42 absorption of zinc and non-heme iron because of higher phytate. Almost no interventional trials have
43 studied iron or zinc status, and our knowledge is based on modelling (12).

44 Studies modeling healthier diets generally use constant absorption coefficients for iron and zinc (8,10,13)
45 and seldom take account of variations in their bioavailability induced by dietary changes to modeled diets
46 (14). Furthermore, uncertainties remain regarding the physiological requirements for iron and zinc
47 because of a lack of accurate endpoints or intermediate markers and the considerable variability seen
48 regarding iron requirements, particularly among menstruating females. For instance, the population
49 reference intake for menstruating females (i.e. the amount of iron that covers the requirements of 95% of
50 females) is ~50% higher than the that needed to cover the requirements of 80% of females (10).

51 Furthermore, the prevalence of people with insufficient iron intake compared to the estimated
52 requirement is much higher than the actual prevalence of iron-deficiency anemia, and the clinical impact
53 of insufficient zinc intake has been little characterized in adults. The reference values used for iron and
54 zinc might therefore be over-protective and thus excessively constraining when defining or assessing
55 healthy dietary patterns.

56 During this study, we estimated the amounts of bioavailable iron and zinc in the diets of a reference sample
57 of an adult population in France, which has similar background intakes and reference values for iron and
58 zinc as other western countries (15) and then we used multi-criteria optimization to model healthy eating
59 patterns in order to test the hypothesis that iron and zinc, rather than other nutrients, are important
60 determinants of optimized healthy eating patterns. We then determined whether, and to what extent,
61 meeting iron and zinc reference values limited our ability to identify healthier diets.

62 **Methods**

63 *Input data used for diet modeling*

64 We used food consumption data for males (n=561, 18-64 years old) and pre-menopausal females (n=564,
65 18-54 years old) classified as non-under-reporters in the French INCA3 national study conducted in 2014-
66 2015. The survey design and methods have been described in full elsewhere (16,17). The socio-
67 demographic characteristics and lifestyles of the study population are presented in **Table 1**. Briefly, food
68 and beverage intake were assessed using three unplanned non-consecutive 24h-dietary recalls collected
69 by trained interviewers assisted by dietary software. Portion sizes were estimated using validated
70 photographs (16). Nutrient intake was calculated using the 2016 nutritional composition database from
71 the French *Centre d'Information sur la Qualité des Aliments; CIQUAL* (18). Food items (n=1533) were
72 categorized into 45 food groups (10)(Supplemental Table 1). In each food group, the nutrient composition
73 (for 41 nutrients) was calculated as a composite composition by gender, being the average nutrient
74 composition of the group food items weighted by their average gender-specific population intake. Using
75 three 24h-recall provides low precision for the individual estimates of intakes for nutrients that are little
76 evenly distributed within individual diets (e.g. vitamin A and vitamin B12) but provides a good precision
77 for estimating the average and inter-individual variability of intakes in a population for most nutrients,
78 including iron and zinc. Furthermore, remaining error related to the intra-individual variability of intake
79 for iron and zinc was addressed by extraction when assessing usual intake, as presented below.

80 *Iron and zinc bioavailability*

81 We first of all considered heme iron (mainly present in red meat) and non-heme iron (present in other
82 animal-based and plant-based foods)(19). The following equation was used for the absorption of heme
83 iron (20):

$$84 \text{ Log Absorption (\%)} = 1.9897 - 0.3092 \times \log (\text{SF})$$

85 where SF is serum ferritin, which was set at 15 µg/L (15). A serum ferritin value of 15 µg/L corresponds to
 86 an absence of iron reserve and a higher intestinal absorption, without any further functional impact (21).
 87 This value, as compared to 30 µg/L, leads to a better estimate of iron absorption at marginal levels of iron
 88 intake. It also provides the lowest estimate of iron requirement, which is the least favourable situation for
 89 our hypothesis that current estimates of iron requirement limit the identification of healthier diets.

90 For non-heme iron, we used the following equation (22):

$$91 \quad \text{Ln Absorption (\%)} = 6.294 - 0.709 \ln(\text{SF}) + 0.119 \ln(\text{C}) + 0.006 \ln(\text{MFP} + 0.1) \\ 92 \quad - 0.055 \ln(\text{T} + 0.1) - 0.247 \ln(\text{P}) - 0.137 \ln(\text{Ca}) - 0.083 \ln(\text{NH})$$

93 where SF is serum ferritin which was also set at 15 µg/L, C is vitamin C (mg), MFP is meat, fish, and poultry
 94 (g), T is tea (number of cups), P is phytate (mg), Ca is calcium (mg), and NH is non-heme iron (mg).

95 For zinc absorption, we used the following equation (23):

$$96 \quad \text{TAZ} = 0.5 \times \left\{ 0.033 \times \left(1 + \frac{\text{TDP}}{0.68} \right) + 0.091 + \text{TDZ} - \sqrt{\left(0.033 \times \left(1 + \frac{\text{TDP}}{0.68} \right) + 0.091 + \text{TDZ} \right)^2 - 4 \times 0.091 \times \text{TDZ}} \right\}$$

97 where TAZ is bioavailable zinc (mmol), TDZ is dietary zinc (mmol) and TDP is dietary phytate (mmol).

98 *Multi-criteria optimization of the diet*

99 A multi-objective, non-linear, constrained optimization program was developed using the optmodel
 100 procedure under SAS software (SAS Institute®, Inc., Cary, NC, USA, version 9.4). The decision variables
 101 were the average daily consumptions of the 45 food groups. We considered male and female populations,
 102 the latter being divided into two subpopulations as a function of their iron requirement levels (Fe- or Fe+
 103 females). Indeed, ~80% of pre-menopausal females have "low-to-medium" iron requirements (Fe-) that
 104 are covered by 1.72 mg/d bioavailable iron, and 20% have "high" iron requirements (Fe+) that are covered
 105 by 2.52 mg/d (10).

106 The optimization procedure consisted in maximizing the health quality of the modeled diet while
 107 simultaneously minimizing its deviation from the current diet. We therefore drew upon the multi-criteria
 108 diet optimization method developed in a previous study by the French Agency for Food, Environmental
 109 and Occupational Health & Safety (ANSES) on Healthy Eating Pattern modelling for French FBDG (10),
 110 which considered two sub-functions in the objective function. On the one hand, the *Health* sub-function
 111 set as its objective compliance with dietary recommendations derived from epidemiological knowledge
 112 on the associations between the consumption of certain food groups and the risk of chronic diseases (24–
 113 27). The *Health* sub-function was defined as consumptions to be reduced (red meat including offal,
 114 processed meat and sweetened beverages), as well as those to be increased (whole grain products, fruit
 115 and vegetables) in accordance with current French recommendations (24). The *Health* objective sub-
 116 function was thus expressed and maximized as follows:

$$117 \quad \text{Max Health} = \sum_{i=1}^3 \left[\frac{\text{Opt}(i)}{\text{P95}(i)} \right] - \sum_{j=1}^3 \left[\frac{\text{Opt}(j)}{\text{Max}(j)} \right]$$

118 Where i is the number of food groups to increase (whole grain products, fruit and vegetables), j is the
 119 number of food groups to decrease (red meat, processed meat and sweetened beverages), $\text{Opt}(i)$ and
 120 $\text{Opt}(j)$ are the optimized consumptions of food groups i and j , respectively (in g/d), $\text{P95}(i)$ is the current
 121 95th percentile of consumption of food group i (in g/d) and $\text{Max}(j)$ is the upper limit of consumption of the
 122 food group as defined by ANSES (in g/d).

123 On the other hand, the *Diet Departure* sub-function was used to minimize the difference between the
 124 optimized and observed food quantities in order to account for the dietary habits of the population. This
 125 *Diet Departure* sub-function was defined as the sum of the squares of the differences for each group
 126 between observed and optimized consumptions standardized by their standard deviations in the observed
 127 diets. We chose such a quadratic formulation (with the squares of differences) in order to favor numerous

128 small changes across a large number of food groups, rather than a few major changes (28). The *Diet*
 129 *Departure* sub-function was thus expressed and minimized as follows:

$$130 \quad \text{Min Diet Departure} = \sum_{k=1}^n \left[\frac{\text{Obs}(k) - \text{Opt}(k)}{\text{SD}(k)} \right]^2$$

131 Where k is the total number of food groups, $\text{Obs}(k)$ and $\text{Opt}(k)$ are the observed and optimized
 132 consumptions of food group k (in g/d), respectively, and $\text{SD}(k)$ is the observed standard deviation of the
 133 consumption of food group k .

134 Because some food groups were considered to be more easily interchangeable, they were grouped
 135 together in the *Diet Departure* sub-function so as to avoid penalizing these substitutions. These non-
 136 penalized substitutions involved those between different kinds of fruit (fresh/dried/processed), breads
 137 (refined/whole grain), other starches (refined/whole grain), vegetable fats (low/high in α -linolenic acid),
 138 meat (poultry/red meat, excluding offal), sweetened beverages (beverages with added sugar/fruit juices),
 139 fish (fat/lean), fresh dairy products (natural/sweetened), and soups/bouillons.

140 *Nutritional constraints*

141 A large set of nutritional constraints was applied to ensure that all nutrients requirements were covered,
 142 as well as a few dietary constraints relative to certain specific food groups under Food-Based Dietary
 143 Guidelines (FBDG). Nutrient constraints differed for some nutrients depending on the sub-population
 144 considered (males, Fe- females, Fe+ females) and were based on the recently revised ANSES Reference
 145 Values (15) (**Table 2**). One exception was vitamin D, for which we did not set any lower constraint, because
 146 the reference value is known to be much too high to permit a solution from diet optimization, as the
 147 observed dietary intake is only ~20% of the reference value and diet is not the sole source of body vitamin
 148 D (10). Dietary constraints were the upper bounds for food groups that had to be reduced according to
 149 the *Health* objective sub-function (i.e., their upper limits of consumption): 71 g/d for red meat (i.e. ~500

150 g/week (24)), 25 g/d for processed meat, and 2,63 g/d (i.e. the average portion size) for sweetened
151 beverages (juices, nectars and soft drinks) (10).

152 *Acceptability constraints*

153 Acceptability constraints were used to keep the modeled consumptions per food group within the range
154 observed in each sub-population (males, Fe- females, Fe+ females; Supplemental Table 2). Acceptability
155 constraints included lower and higher values, corresponding to the 5th or 95th percentiles of consumption
156 for all food groups, except those whose upper limit was set as a dietary constraint (red meat, processed
157 meat and sweetened beverages – see above). In the acceptability constraints, in the same way as for the
158 *Diet Departure* sub-function, the most substitutable food groups (see above) were grouped together to
159 define their lower and upper bounds as the 5th or 95th percentiles of their total consumption.

160 *Standardization of constraints to compare their relative influences*

161 We estimated the dual values associated with each constraint; i.e. estimates of the potential gain in
162 objective function that would result from relaxing by one unit the limiting bound of the considered
163 constraint. All constraints were standardized on the value of their limiting bounds (29), so that the
164 standardized dual values (representing the effect of a 100% relaxation of the limiting bound) could be
165 compared numerically with each other, and the limiting (i.e., active) constraints for nutrient and food
166 group intakes classified from the most to the least limiting.

167 *Optimization models without or with flexibility on the nutrient constraints for zinc and iron*

168 We finally used a standard optimization model (Non-Flexible, NFlex) and an alternative optimization model
169 allowing flexibility on bioavailable iron and zinc (Flexible, Flex), the latter having been identified as the
170 most binding nutrient constraints in the standard model. This alternative optimization model was
171 developed with goal programming rather than strict constraints on these nutrient intakes in order to study

172 how the estimated requirements for bioavailable iron and zinc would drive and impact the composition of
173 the modeled diets. Flexibility regarding zinc and iron intakes was thus introduced by replacing their
174 nutrient constraints with a new goal variable added to the objective function, in order to minimize
175 violation of the relaxed nutrient constraints while concomitantly maximizing the *Health* and minimizing
176 the *Diet Departure* sub-functions. For safety reasons, new lower threshold values for bioavailable zinc and
177 iron were also introduced as constraints and set as deficiency threshold corresponding to the minimum
178 intake that would limit the probability of a nutritional deficiency, as previously described (30). The
179 bioavailable zinc deficiency threshold was set at 1.6mg in males and 1.3mg in females (30). The
180 bioavailable iron deficiency threshold was recalibrated to match the prevalence of iron-deficiency anemia
181 in the French population. The distribution of bioavailable iron was log-transformed, and the usual
182 bioavailable iron distribution was derived by extracting the intra-individual variation using the Nusser
183 method (31). We then used the probabilistic approach (32) with Monte-Carlo simulation to estimate the
184 number of individuals with bioavailable iron levels below the requirement, based on the modeled
185 distribution of usual bioavailable iron and a risk curve obtained from the cumulative distribution of the
186 requirement as modelled during an earlier work (33) and by ANSES (34). The risk curve was then
187 recalibrated by translation to obtain prevalence estimates that matched the actual prevalence of iron-
188 deficiency anemia in the French population (i.e. 0.2% in males and ~4% in females)(35). The deficiency
189 threshold was set at the 97.5th percentile of this recalibrated risk curve, and the values obtained for males
190 and females are indicated in Table 2.

191 As a complementary analysis, we also ran the two optimization models (without or with flexibility on
192 bioavailable iron and zinc) while suppressing the *Diet Departure* term in the objective function (NFlex+ and
193 Flex+, respectively), in order to test whether the effect of flexibility (i.e., between-model differences)
194 would remain similar when allowing any diet change without penalization.

195 *Characterizing the expected health impact of modeled diets*

196 The EpiDiet model was used to evaluate the health benefits of the modeled diets within each optimization
197 model (NFlex and Flex), assessing expected changes in death rates, chronic disease risks and disease
198 burden as the number of years of life lost that would be avoided if French adults would replace their
199 observed diet with the considered modeled diet (36,37). EpiDiet is a simulation-based nutritional and
200 epidemiological model previously developed by our group (37) that implements the comparative risk
201 assessment framework. Like many other such risk assessment models (38,39), it quantifies the positive or
202 negative changes in risk related to long-term health that would result from changes to the average diet
203 for an individual, groups or population. In this study, we considered the observed diet in the French
204 population as the baseline situation and the modeled diets obtained with the NFlex and Flex optimization
205 models as counterfactual situations. We considered the food and nutrient intakes of males and females,
206 grouping together Fe- and Fe+ females according to their 80:20 proportions in the population (see above).
207 Uncertainty Intervals on health estimates, corresponding to the precision of the parameters of the EpiDiet
208 model, were computed using Monte Carlo simulations. Details of the EpiDiet model and its application are
209 presented in Supplemental Method 1.

210 We also evaluated changes in the prevalence of iron-deficiency anemia that might be attributable to
211 changes in bioavailable iron intake in the modeled diets, using the probabilistic approach. Bioavailable iron
212 distribution was modeled by translating the modeled distribution of usual absorbed iron (see above)
213 according to the difference between mean intakes for each sex and modeled diet, and used the sex-specific
214 recalibrated risk curve for iron-deficiency anemia, as described above. Confidence Intervals were build
215 taking into account sampling error and a binomial distribution.

216 Finally, we estimated the burden of disease as Disability Adjusted Life Years (DALYs) averted or added and
217 corresponding to changes in the risks of cerebrovascular diseases, ischemic heart diseases, diabetes and
218 colorectal cancer on the one hand, and changes in estimates of the prevalence of iron-deficiency anemia
219 on the other hand, for the diets modeled using each optimization model (see Supplemental Method 1).

220 **Results**

221 *Standard non-flexible (NFlex) optimization model*

222 Compared to the observed diets, the modeled diets obtained using the first, non-flexible (NFlex)
223 optimization model were characterized by healthier dietary patterns (**Figure 1**) due to some gains in the
224 *Health* criteria at the cost of some deterioration in the *Diet Departure* criteria (**Table 3**). These healthier
225 dietary patterns involved a large substitution of refined grain products (with variations of -56% to -95%
226 between the different sub-populations) with whole grain products, with a total grain product consumption
227 that remained generally unchanged, alongside an increase in fruit and vegetable consumption (+45% to
228 +71%), a reduction in processed meats (-17% to -100%) and in soft drinks among males (Supplemental
229 Table 3). Total red meat consumption remained almost unchanged in males (-10%) but increased markedly
230 among females (+67%) with a particular increase in offal consumption by Fe+ females. By contrast, poultry
231 increased in males and Fe+ females (+250% and +247%, respectively, but -33% in Fe- females), so that total
232 meat consumption was finally almost similar in males (+11%) and Fe- females (+1%) but markedly
233 increased in Fe+ females (+98%).

234 Whatever the population, the most limiting constraints with the greatest impact on the composition of
235 modeled diets were bioavailable iron and zinc constraints, which displayed higher dual values than those
236 for all other constraints affecting nutrients or food groups (Table 3). In the modeled versus the observed
237 diets, covering nutrient reference values led to increases in bioavailable zinc and iron that were marked
238 among Fe- females (+42% for iron and +6% for zinc) and even greater in Fe+ females (+108% for iron and
239 +21% for zinc) (**Figure 2** and Supplemental Table 4). Reaching zinc reference values was more constraining
240 in males while meeting iron reference value was more constraining in females and particularly in Fe+
241 females where it required the most important dietary changes (as can be seen from their higher *Diet*
242 *Departure* value). In addition, the constraints on zinc and iron worked together by involving similar dietary

243 changes, even if the most limiting constraint in each gender (namely, zinc in males and iron in females)
244 was so predominant that it masked the influence of the other. In males, the influence of the iron
245 requirement could be revealed when relaxing the zinc requirement, and *vice versa* in females (results not
246 shown).

247 *Alternative flexible (Flex) optimization model*

248 Under the alternative optimization model (Flex), flexibility was applied simultaneously to the constraints
249 on bioavailable iron and zinc because of their inter-dependency. When compared to both the observed
250 and NFlex-modeled diets, Flex-modeled diets contained less meat, and particularly less red meat, and
251 more grain products, and notably more whole grain products (Figure 1). As compared to NFlex, the Flex
252 modeling option did result in a reduction in red meat (-87% to -91% vs observed, i.e., a massive and similar
253 reduction whatever the population) (Supplemental Table 3), and a further increase in whole grain products
254 (+97% in males, -3% in Fe- females, +153% in Fe+ females, vs NFlex). Unlike with the NFlex-modeled diets,
255 total meat in the Flex-modeled diets was globally similar to that of the observed diet, as poultry was also
256 increased less in males and Fe+ females, and total red meat was reduced more in females.

257 Compared to the NFlex option, the Flex option accordingly resulted in better *Health* criteria together with
258 lower *Diet Departure* criteria (Table 3), since fewer dietary changes were required to cover the lower zinc
259 and iron constraints that were by construct between the nutrient reference values and the deficiency
260 thresholds. In the Flex-modeled diets, bioavailable zinc and iron were respectively 20% and 30% lower
261 than their reference values in males, 14% and 37% lower in Fe- females and 14% and 57% lower in Fe+
262 females (Table 3, Figure 2 and Supplemental Tables 3 and 5).

263 In the Flex optimization model, i.e. when relaxing the constraints on bioavailable iron and zinc, we found
264 that six nutritional constraints were limiting, namely (and in decreasing order of importance) sodium,
265 iodine, saturated fatty acids, α -linolenic acid, fiber and vitamin A (Table 3). Sodium was the most limiting

266 constraint in both sexes, followed by α -linolenic acid and saturated fatty acids in males and iodine and
267 saturated fatty acids in females.

268 *Estimate of changes to the disease burden resulting from modeled diets*

269 We estimated that in French adults, the mortality risk from ischemic heart diseases, cerebrovascular
270 diseases, diabetes and colorectal cancer would be reduced by 22% in males and 15% in females with the
271 NFlex-modeled diets, and by 26% in males and 23% in females with the Flex-modeled diets (**Table 4** and
272 Supplemental Table 6). We also estimated that the burden of these diseases would be reduced by 24% in
273 males and 15% in females by the NFlex-modeled diets and by 28% in males and 25% in females by the Flex-
274 modeled diets (Supplemental Table 7). When compared to the NFlex optimization, the Flex optimization
275 thus resulted in a further decrease in the burden of these diseases of 19% in males (+13,654 DALYs averted)
276 and 70% in females (+7,131 DALYs averted) (Table 4). By contrast, being more flexible with iron and zinc
277 reference values would also tend to increase the prevalence of iron-deficiency anemia (from 2.1% (95%
278 CI: 1.4%, 3.9%) currently to 5.0% (3.9%, 6.4%) in adults, from 0.21% (0.04%, 0.98%) currently to 3.0% (1.8%,
279 4.6%) in males, and from 3.9% (2.6%, 5.9%) currently to 7.0% (5.1%, 9.4%) in females), whereas the figures
280 would be virtually null without flexibility (0.11% (0.02%, 0.49%) in adults, 0.17% (0%, 0.65%) in males and
281 0.05% (0%, 0.66%) in females). However, the DALYs resulting from this increase in iron-deficiency anemia
282 with flexibility (Flex vs NFlex) would be small compared to the DALYs otherwise averted by the decrease
283 in chronic disease (2,705 vs 13,654, *i.e.* 20% in males and 3,157 vs 7,131, *i.e.* 44% in females) (Table 4).
284 Globally, when taking account of all these chronic diseases and anemia and on average over the whole
285 population, the Flex optimization resulted in a further 18% reduction in the burden of disease compared
286 to the NFlex optimization (+14,921 DALYs averted).

287 The expected reduction in mortality and disease burden with Flex-modeled diets versus NFlex-modeled
288 diets was mostly ascribed to the reduction in red meat consumption (Supplemental Tables 6 and 7). The
289 increase in whole grain products in Flex- versus NFlex-modeled diets did not therefore result in any

290 additional risk reduction under the comparative risk assessment model. The changes in mortality risk
291 resulting from the changes to red meat consumption were a 3% increase in females under the NFlex option
292 but a 5% decrease in both males and females under the Flex option, while the changes to mortality risks
293 resulting from increases in whole grain products were a similar 5% reduction in both males and females
294 with both options (see Supplemental Table 6). Changes to the risk of morbidity related to cerebrovascular
295 diseases, ischemic heart diseases, diabetes and colorectal cancer due specifically to red meat involved a
296 3% increase in females under the NFlex option but a 5-6% decrease in both males and females under the
297 Flex option, while the changes to these morbidity risks specifically due to an increase in whole grain
298 consumption were a similar 4-5% decrease in both males and females with both options (see Supplemental
299 Table 7). Soft drinks were another food group whose variations between the observed and modeled diets
300 significantly affected the risks of mortality and morbidity, but soft drinks varied less between the NFlex
301 and Flex options than red meat and whole grain products, and the changes in mortality and morbidity risks
302 due specifically to a reduction in soft drink consumption were a similar 6-8% decrease with both options
303 (see Supplemental Tables 6 and 7).

304 *Additional models to test the impact of Diet Departure criteria*

305 We also ran additional models with optimization without the *Diet Departure* criteria (i.e., with optimization
306 on the *Health* criteria only), without or with flexibility on bioavailable zinc and iron (NFlex+ and Flex+
307 models, respectively). They all led to healthier dietary patterns than their standard counterparts that
308 included the *Diet Departure* criteria, by further notable increases in the consumption of fruit and
309 vegetables and whole grain products (Supplemental Figure 1 and Supplemental Tables 3 and 5). The
310 differences between Flex+ and NFlex+ were similar to those previously observed between Flex and NFlex
311 with regard to diet contents in red meat (only reduced under Flex+ and not under NFlex+) and whole grains
312 (further increased in Flex+ compared to NFlex+), and also with regard to the amounts of bioavailable iron
313 and zinc that were similarly reduced in the event of flexibility, whether the *Diet Departure* criteria were

314 integrated or not (Supplemental Figure 2). Lastly, the dual values analysis showed that like the NFlex and
315 Flex models, the most limiting constraint for healthier diets were bioavailable iron and zinc in the NFlex+
316 model, and sodium, iodine, vitamin A, energy intake, docosahexaenoic acid (DHA) and eicosapentaenoic
317 acid (EPA) in the Flex+ model (Supplemental Table 8).

318 **Discussion**

319 Our study has revealed a conflict between meeting current estimates for iron and zinc requirements that
320 take account of their bioavailability, and implementing a healthy diet. We have indeed shown that in males
321 and females, securing iron and zinc provisions precludes a reduction in red meat consumption and limits
322 any increase in whole grains. By contrast, both of these goals can be achieved by allowing some flexibility
323 regarding current reference values for bioavailable iron and zinc which leads to contrasted effects on
324 health (more anemia but less chronic disease) but a better overall balance (18% more DALYs averted with
325 flexibility than without).

326 Without flexibility, we have shown by dual value analysis that bioavailable iron and zinc were always the
327 most limiting nutrients when modeling healthier dietary patterns, in both males and females and whether
328 or not account was taken of dietary cultural inertia (standard NFlex and additional NFlex+ models). This
329 conflict between meeting the estimated requirements for bioavailable iron and zinc and adopting healthier
330 dietary patterns therefore appears to concern all populations and prevailing dietary contexts. We have
331 also shown that this limitation, and the effect of it being removed by flexibility, was further accentuated
332 when considering females with high iron requirements. In this case, the very high target value for
333 bioavailable iron fully precluded any reduction in red meat and also largely limited the increase in whole
334 grains (because of their phytate content that limits iron bioavailability). Although the nutrients with the
335 greatest influence were zinc in males and iron in females, in all cases zinc and iron were the two most
336 influential nutrients and worked together by driving similar dietary changes. This could be explained by
337 the fact that the dietary contributors of iron intake are mostly the same as those of zinc, and iron and zinc
338 absorption are both largely dependent on phytate (2,3).

339 Animal products, and particularly meat and red meat, are known to be important contributors of iron and
340 zinc intakes, and iron requirements are known to be high for the top quintile of females of childbearing

341 age, whereas the phytate content in plants is well known to largely inhibit non-heme iron and zinc
342 absorption (40,41). Yet there are few data in the literature which characterize the importance of this
343 expected conflict when dealing with the transition toward diets with a higher plant-based content. In
344 particular, there have been almost no published studies on diet modeling and optimization on health
345 criteria that account for iron or zinc bioavailability. In a diet optimization study on environmental criteria,
346 designed to decrease diet-induced environmental pressures that also require a reduction in red meat
347 consumption, Barre et al. showed that including bioavailability factors tended to limit the reduction in red
348 and processed meats (14). The model used by these authors integrated 402 food items in the same French
349 context, whereas in the present model we focused on 45 food groups that prevented the selection of
350 individual food items that were atypical within their group. The smaller decrease in processed meat when
351 accounting for bioavailability indicated by Barre et al. (14) was indeed ascribed to a dramatic increase in
352 the consumption of blood sausage (a processed meat specialty made from pork blood), which was
353 sufficient to cover the iron reference value (88% of heme iron was sourced by this increase in blood
354 sausage consumption according to Barre et al., while blood sausage accounted for only 1.5% of its food
355 group (processed meat) consumption in our study). Ferrari et al. (42) also found that in females, the
356 constraint related to iron requirement was incompatible with a constraint limiting red meat consumption,
357 but these authors considered iron intake and not bioavailable iron (42) in females with low iron intakes.
358 Unlike iron, the importance of zinc when considering healthy dietary patterns has been little emphasized.
359 This can again be ascribed to the paucity of data considering zinc absorption in diet modeling, and also by
360 the fact that it remains difficult to define zinc requirements using health-based criteria, as it remains
361 difficult to assess zinc status. Although the important effect of phytate on zinc absorption is well
362 documented (43), and sources of zinc are animal-based, and evidence for altered zinc status in vegetarians
363 is unclear (4). No adequate biomarkers for zinc status are available to derive requirement estimates.

364 Furthermore, zinc requirements have been estimated using a factorial approach to considering
365 physiological requirements by estimated total daily losses and zinc absorption coefficients (44).

366 The strength of our work was therefore that it evidenced and characterized the importance of the conflict
367 between iron and zinc on the one hand, and red meat and whole grain consumption on the other. This
368 conflict stems from the importance of red meat as a contributor to iron and zinc, and the importance of
369 whole grains in decreasing iron and zinc absorption because of phytate. This work has also highlighted the
370 importance of uncertainties regarding iron and zinc absorption and phytate contents in foods. In particular,
371 major modeling efforts have been made to predict iron and zinc bioavailability in diets, but uncertainties
372 remain (12,14,45).

373 Because iron and zinc are so important to defining healthy eating patterns that can be used to build Food-
374 Based Dietary Guidelines (FBDG), a precise assessment of iron and zinc requirements and their
375 recommended dietary allowances is a primary concern. Iron and zinc reference values are based on
376 physiological requirements assessed from estimates of mandatory losses. For zinc, again, an adequate
377 marker of status is lacking, and it is difficult to ascertain its relevance to health. There are considerable
378 variations in iron requirements among females, and this has led to a very high recommended dietary
379 allowance in order to cover 95% of them whereas most (80%) have much lower requirements. According
380 to these requirements, iron insufficiency does not match actual iron deficiency as assessed by iron-
381 deficiency anemia. For example, among French females, the prevalence of iron-deficiency anemia has
382 been estimated at ~4%, while 20% of females have iron intakes below their requirements and most have
383 intakes below the population reference intake (10). As demonstrated by Hallberg et al., non-heme iron
384 absorption is higher in populations that are vulnerable to iron deficiency (46). The risk of iron-deficiency
385 anemia could therefore be taken as a safeguard which would lead to a much lower reference target value,
386 indeed as low as the deficiency threshold we used in the model with flexibility (Flex). The provision of iron
387 at higher levels than this threshold may also have health benefits in preventing iron deficiency without

388 anemia. However, the adverse health effects of iron deficiency have been poorly characterized in literature
389 studies, due to small sample sizes, confounding by other dietary and lifestyle factors, and by alterations in
390 iron metabolism in response to infection. Furthermore, thresholds of iron deficiency at which these
391 adverse effects might develop have not been well characterized and their prevalence in western countries
392 is unknown (47). Clearly, further research is needed to characterize the relationship between iron intake
393 and iron deficiency without anemia in adults in western countries, and evaluate its importance for health.
394 During the present study, we found that waiving the importance of iron and zinc in the Flex model brought
395 bioavailable iron levels down to the deficiency threshold we used in females, which would translate into
396 an increase in the prevalence of iron-deficiency anemia among females from ~4% at present to 7% under
397 the modeled diets. This contrasted with the virtual absence of iron-deficiency anemia (0.05%) in the diets
398 modeled without flexibility (NFlex) that imposed a reference value for bioavailable iron in Fe+ females that
399 was triple the deficiency threshold. To further assess the conflict that we have evidenced, this modeled
400 increase in iron-deficiency anemia was weighed against the expected long-term health benefits that would
401 result from adopting a healthier diet, which could help to inform about the importance of the iron
402 reference value. Using the single metric of DALYs averted, we were able to show that the long-term health
403 benefit of diets identified as being flexible with iron and zinc outweighed the adverse effects resulting
404 from the increase in iron-deficiency anemia.

405 Our work has implications for healthy eating modeling and thus dietary guidelines. Iron and zinc absorption
406 have been little studied in this regard. Dietary guidelines usually advocate healthy eating patterns, similar
407 to the diets identified during the present study (including lower red meat and higher whole grain
408 consumption) but with uncertainties regarding the actual benchmark levels for meat and red meat (7–9).
409 Likewise, prospective diets for human and planetary health have defined plant-based diets as the
410 reference, but the impact on iron status of such diets has not been fully characterized (10–12). Markedly
411 reducing red meat and increasing whole grains imply lowering levels of bioavailable iron and zinc, and the

412 ensuing risk of an increase in iron-deficiency anemia. This risk may be deemed acceptable if outweighed
413 by the clearly beneficial effects of healthier dietary patterns on chronic diseases with very high prevalence.
414 This risk may also be acceptable if it can be mitigated. Indeed, in developed countries, iron-deficiency
415 anemia can be detected and treated on an individual basis, and could also be prevented by food
416 fortification at the population level (48).

417 *Strengths and limitations*

418 Our study had certain strengths and limitations. One strength was the use of data and equations to
419 monitor bioavailable iron and zinc in the modeled diets, but these bioavailability estimates involved some
420 uncertainties (49,50). A second strength was the use of advanced optimization models with multi-criteria
421 optimization by nonlinear programming, in order to identify the food groups and nutrient-related factors
422 that hinder or favor healthier dietary patterns. However, in terms of limitations, diet modeling and
423 optimization can exacerbate uncertainties and are reliant on a complex definition of constraints and
424 objectives, which often involves an implicit weighting of numerous criteria (10). For instance, regarding
425 the constraint on bioavailable iron, although we used the most accurate estimates available, some
426 uncertainty remained in the equation used to calculate its absorption and in the estimate of the deficiency
427 threshold we used in the case of flexibility. The number of food groups also greatly influenced the model
428 by smoothing the nutritional contents of the groups and thus masking any specificity of certain
429 contributors within each group, at a more detailed level. However, the food groups in the modeled diet
430 remained interpretable because they continued to reflect the true food consumption at present within
431 these groups. Lastly we used recent, representative data for food consumption, with a sample size
432 ($n=1,125$) that may appear to be low. A higher sample size would have been useful for better characterizing
433 the variability of the dietary patterns in the population, but since the study mainly relies on modelled shifts
434 in average intakes from observed diets using optimization models, the sample size is large enough to

435 provide a good precision for these population estimates and to run nutritional/health impact analysis
436 based on the modeled diets.

437 *Conclusion*

438 Using diet modeling and considering bioavailability, we have evidenced that iron and zinc are the most
439 critical nutritional factors with respect to healthy eating patterns. Lower iron and zinc intakes from a lower
440 consumption of meat (especially red meat) and a higher phytate intake from eating more plant-based
441 products (especially whole grains) result in low bioavailable iron and zinc in modeled diets that tend to
442 limit the overall health benefits of the healthiest dietary patterns. Our results highlight the predominance
443 of iron and zinc reference values in diet modeling for Food-Based Dietary Guidelines.

444

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TABLE 1 Lifestyle and sociodemographic characteristics of the sample of adults ($n = 1,125$) extracted from the French national INCA3 study, 2014-2015.

	Males ($n = 564$)	Females ($n = 561$)
Age, %		
< 25y	9%	8%
25-35y	16%	25%
35-50y	38%	52%
50-65y	37%	15%
Level of education, %		
< High-school diploma	34%	23%
High-school diploma	21%	21%
Post-secondary graduation	44%	56%
Body Mass Index, %		
< 18.5 kg·m ⁻²	2%	4%
18.5-24.99 kg·m ⁻²	49%	59%
25-29.99 kg·m ⁻²	38%	24%
> 30 kg·m ⁻²	11%	12%
Alcohol consumption, %		
Non-drinker	30%	54%
Moderate drinker ¹	70%	46%
Heavy drinker	-	-

¹ <20g/d for females and <30 g/d for males)

TABLE 2 Nutritional constraints used in the optimization models

Nutrient	Unit	Lower bounds ¹		Upper bounds ²	
		Males (18-64 y)	Females (18-54 y)	Males (18-64 y)	Females (18-54 y)
Energy intake ³	kcal·d ⁻¹	2,470	1,995	2,730	2,205
Retinol	µg·d ⁻¹	-	-	3,000	3,000
Vitamin A	µg·d ⁻¹	750	650	-	-
Thiamin	µg·(kcal·d) ⁻¹	0.418	0.418	-	-
Riboflavin	mg·d ⁻¹	1.6	1.6	-	-
Niacin	mg NE·(kcal·d) ⁻¹	0.0067	0.0067	-	-
Pantothenic acid	mg·d ⁻¹	3.77	3.22	-	-
Vitamin B6	mg·d ⁻¹	1.7	1.6	25	25
Folate	µg·d ⁻¹	330	330	-	-
Vitamin B12	µg·d ⁻¹	4	4	-	-
Vitamin C	mg·d ⁻¹	110	110	-	-
<i>Vitamin D</i>	µg·d ⁻¹	-	-	100	100
Vitamin E	mg·d ⁻¹	5.28	4.37	-	-
Vitamin K1	µg·d ⁻¹	39.47	34.48	-	-
Calcium	mg·d ⁻¹	950	950	2,500	2,500
Copper	mg·d ⁻¹	1.07	0.89	5	5
Bioavailable iron - NFlex model ⁴	mg·d ⁻¹	1.72	1.72 or 2.52 ⁵	-	-
Bioavailable iron - Flex model ⁴	mg·d ⁻¹	0.83	1.08	-	-
Iodine	µg·d ⁻¹	150	150	600	600
Magnesium	mg·d ⁻¹	254	195	-	-
Manganese	mg·d ⁻¹	1.99	1.52	-	-
Phosphorus	mg·d ⁻¹	550	550	-	-
Potassium	mg·d ⁻¹	3,500	3,500	-	-
Selenium	µg·d ⁻¹	70	70	300	300
Sodium	mg·d ⁻¹	1,500	1,500	2,300	2,300
Bioavailable Zinc - NFlex model ⁴	mg·d ⁻¹	3.63	3.23	25	25
Bioavailable Zinc - Flex model ⁴	mg·d ⁻¹	1.6	1.3	25	25
Water	g·d ⁻¹	2,500	2,000	-	-
Saturated fatty acids	%EI·d ⁻¹	-	-	12%	12%
Lauric, myristic and palmitic acids	%EI·d ⁻¹	-	-	8%	8%
Linoleic acid	%EI·d ⁻¹	4%	4%	-	-
α-linolenic acid	%EI·d ⁻¹	1%	1%	-	-
Linoleic acid : α-linolenic acid	-	-	-	5	5
EPA+DHA ³	g·d ⁻¹	0.5	0.5	-	-
Sugar excluding lactose	g·d ⁻¹	-	-	100	100
Protein	g·(kg_bw·d) ⁻¹	0.83	0.83	2.3	2.3
Fiber	g·d ⁻¹	30	30	-	-

¹ Lower bounds are the Population Reference Intake or lowest value of the macronutrient reference intake range.

² Upper bounds are the Tolerable Upper Intake Level or highest value of the macronutrients reference intake range.

³ Deficiency thresholds. DHA, docosahexaenoic acid; EI, energy intake; EPA, eicosapentaenoic acid. 1 kcal = 0.0042 MJ. ⁴NFlex, standard multicriteria optimization model; Flex, goal programming option allowing flexibility regarding

nutrient constraints for zinc and iron. ⁵for females with low-to-medium (Fe- females) / high (Fe+ females) iron requirements.

TABLE 3 Values of the objective sub-functions used during optimization in males, females with low-to-medium iron requirements (Fe-), and females with high iron requirements (Fe+), using the standard multicriteria optimization model (NFlex) or the goal programming option allowing flexibility regarding nutrient constraints for zinc and iron (Flex)

	Males			Females Fe-			Females Fe+		
	Observed diet	Modeled diets		Observed diet	Modeled diets		Observed diet	Modeled diets	
		NFlex	Flex		NFlex	Flex		NFlex	Flex
Objective sub-functions ¹									
Health	-3.18	0.17	1.04	-1.78	-0.44	0.80	-1.78	-1.53	0.81
Diet Departure	0.00	5.32	3.43	0.00	4.63	3.12	0.00	65.18	3.13
Goal		0.00	0.50		0.00	0.51		0.00	0.71
Deviations from requirements ²									
Bioavailable iron		0.00	0.30		0.00	0.37		0.00	0.57
Bioavailable zinc		0.00	0.20		0.00	0.14		0.00	0.14
Dual values of nutrient constraints ³									
Bioavailable zinc		34	0		0	0		0	0
Bioavailable iron		4	0		23	0		645	0
Sodium		-10	-8		-12	-8		-57	-8
Iodine		0	2		13	7		0	7
Saturated fatty acids		-3	-3		-2	-5		0	-5
Alpha-linolenic acid		4	4		5	4		9	4
Fiber		9	1		7	4		13	4
Vitamin A		2	3		1	4		0	4

¹Multi-criteria optimization consisted in maximizing the Health criteria while minimizing the Diet Departure and Goal criteria, with the Goal criteria being the sum of the goal variables regarding bioavailable zinc and iron intakes. ²Relative deviations from reference values (e.g. bioavailable iron = 0.30 means that the value is 30% below requirement), whose sum is equal to the Goal criteria. ³Standardized dual values representing the potential effect of a 100% relaxation of the limiting bound of the constraint considered, to classify the nutritional constraints from the most to the least limiting (i.e., active). Limiting constraints have a positive (negative) value if the lower (upper) bound is binding. Only nutrients with a limiting

constraint (i.e. with a non-null dual value) are presented here. For each scenario, the most limiting constraint (i.e., with the highest absolute value) is in bold.

TABLE 4 Expected changes to mortality and morbidity in French adults resulting from the adoption of modeled diets as compared to observed diets

	Adults (over 18 y)		Males (18-64 y)		Females ¹ (18-54 y)	
	Modeled diets		Modeled diets		Modeled diets	
	NFlex	Flex	NFlex	Flex	NFlex	Flex
Decrease in mortality risk, % (95%UI)^{2,3}						
Ischemic Heart Diseases	20 (18, 22)	19 (18, 21)	20 (18, 22)	19 (17, 21)	24 (21, 27)	23 (19, 26)
Cerebrovascular Diseases	16 (13, 18)	23 (21, 26)	17 (14, 20)	24 (21, 27)	11 (8, 13)	21 (18, 24)
Diabetes	35 (34, 37)	46 (44, 48)	37 (35, 39)	47 (45, 49)	21 (18, 23)	39 (37, 41)
Colorectal Cancer	23 (21, 25)	31 (29, 34)	26 (23, 28)	33 (31, 36)	12 (10, 14)	24 (22, 26)
Total	21 (19, 23)	25 (24, 27)	22 (20, 24)	26 (24, 28)	15 (13, 16)	23 (21, 25)
DALYs averted (95% UI)^{2,3,4}						
Ischemic Heart Diseases	28,130 (25,581, 30,678)	27,156 (24,648, 29,664)	25,468 (22,942, 27,994)	24,618 (22,133, 27,104)	2,661 (2,324, 2,999)	2,538 (2,200, 2,875)
Cerebrovascular Diseases	14,359 (12,370, 16,348)	21,870 (19,794, 23,945)	11,541 (9,657, 13,426)	16,185 (14,244, 18,127)	2,817 (2,182, 3,453)	5,684 (4,950, 6,418)
Diabetes	22,023 (21,180, 22,865)	29,150 (28,237, 30,064)	19,681 (18,882, 20,479)	24,678 (23,795, 25,562)	2,342 (2,073, 2,611)	4,472 (4,239, 4,705)
Colorectal Cancer	18,708 (17,202, 20,215)	25,827 (24,267, 27,388)	16,379 (14,901, 17,857)	21,241 (19,718, 22,763)	2,329 (2,034, 2,625)	4,587 (4,243, 4,930)
Sub-total	83,220 (79,555, 86,884)	104,003 (100,279, 107,727)	73,069 (69,498, 76,640)	86,723 (83,111, 90,334)	10,150 (9,327, 10,973)	17,281 (16,372, 18,189)
Δ vs NFlex		20,784 (15,559, 26,009)		13,654 (8,574, 18,733)		7,131 (5,905, 8,356)
Iron deficiency anemia	1,548 (1,087, 2,138)	-4,313 (-5,500, -3,169)	30 (27, 129)	-2,675 (-3,556, -1,771)	1,518 (1,060, 2,009)	-1,638 (-1,944, -1,398)
Δ vs NFlex		-5,862 (-7,141, -4,584)		-2,705 (-3,599, -1,811)		-3,157 (-3,705, -2,610)
Total	84,768 (81,066, 88,470)	99,689 (95,787, 103,591)	73,100 (69,528, 76,671)	84,048 (80,327, 87,768)	11,668 (10,718, 12,618)	15,641 (14,693, 16,590)
Δ vs NFlex		14,921 (9,542, 20,300)		10,948 (5,791, 16,105)		3,973 (2,631, 5,315)

¹Food and nutrient intakes of Fe- and Fe+ females, used to estimate changes to risk as compared to the observed situation in females using comparative risk assessment, were averaged according to their 80:20 ratio in the population. ²Estimated changes to the risk of mortality in France comparing diets modeled using different optimization models with the current observed diet in the French adult population. ³95% Uncertainty Intervals (UI) of the estimated impacts were computed from modeled errors in model parameters estimates using Monte Carlo simulations. ⁴DALYs, Disability-adjusted life years averted, comparing diets modeled with different optimization models with the currently observed diet in the French adult population. NFlex, standard multicriteria optimization model; Flex, goal programming option allowing flexibility regarding nutrient constraints for zinc and iron. Uncertainty intervals for averted DALYs are shown in brackets.

Legends for Figures

FIGURE 1 Daily food category consumption in the observed diets (Obs) and modeled diets in males (panel A), females with “low-to-medium” iron requirements (Fe-) (panel B), and females with high iron requirements (Fe+) (panel C), using either the standard multicriteria optimization model (NFlex) or the goal programming option allowing flexibility regarding the nutrient constraints for zinc and iron (Flex)

For clarity, the 45 modeled food groups are not represented here but grouped into broader categories that are included in the Health sub-function (such as red meat, processed meat, soft drinks, grain products, fruit and vegetables) or represent other protein sources (poultry, fish and dairy products), and other food groups have been grouped as “others” (20 groups) and “other drinks” (3 groups). Details are shown in Supplemental Tables 1 and 5.

FIGURE 2 Amount of absorbed iron (upper panel A) and absorbed zinc (lower panel B) under the observed diets (Obs) and modeled diets in males, females with “low-to-medium” iron requirements (Fe-), and females with high iron requirements (Fe+) using either the standard multicriteria optimization model (NFlex) or the goal programming option allowing flexibility regarding nutrient constraints for zinc and iron (Flex)

The solid lines indicate the current reference values for the nutrient and population considered, which are used as the lower bound of the constraint in the NFlex model, and the broken lines indicate the deficiency threshold for the nutrient and population considered that is used as the lower bound of the constraint in the Flex model.