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Title: The Maternal Diet Index in Pregnancy is associated with offspring allergic diseases: The Healthy Start Study

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45 **Abstract**

46

47 **Background:** A systematic review showed limited associations between pregnancy diet and offspring
48 allergy. We developed a maternal diet index during pregnancy that was associated with offspring
49 allergy outcomes.

50

51 **Methods:** Data came from Healthy Start, a Colorado pre-birth cohort of mother/offspring dyads. Food
52 propensity questionnaires were completed during pregnancy. Offspring allergic rhinitis, atopic
53 dermatitis, asthma, wheeze, and food allergy diagnosis up to age four were verified from electronic
54 medical records. Data were randomized into test and replication sets. The index included the weighted
55 combination of variables that best predicted a combined outcome of any allergy in the test set. Index
56 utility was verified in the replication set. Separate adjusted and unadjusted logistic models estimated
57 associations between the index and each offspring allergy diagnosis in the full sample.

58

59 **Results:** The index included weighted measures of intake of vegetables, yogurt, fried potatoes,
60 rice/grains, red meats, pure fruit juice and cold cereals. Vegetables and yogurt were associated with
61 prevention of any allergy, while other components were associated with increased disease. In adjusted
62 models, a one unit increase in the index was significantly associated with reduced odds of offspring
63 allergic rhinitis (odds ratio (CI) 0.82 [0.72-0.94]), atopic dermatitis (0.77 [0.69-0.86]), asthma (0.84
64 [0.74-0.96]), and wheeze (0.80 [0.71-0.90]), but not food allergy (0.84 [0.66-1.08]).

65

66 **Conclusions:** This is the first study that has shown associations between an index of maternal dietary
67 intake during pregnancy and multiple offspring allergic diseases. The results give hope for prevention
68 of allergic diseases *in-utero*.

69

70 **Keywords:** allergic rhinitis, asthma, atopic dermatitis, food allergy, maternal diet index in pregnancy

71

72 **Abbreviations:**

73 ASA Automated Self-Administered

74	AUC	Area under the curve
75	CI	Confidence interval
76	DII	Dietary inflammatory index
77	EAACI	European Academy of Allergy and Clinical Immunology
78	E-DII	Energy-adjusted dietary inflammatory index
79	EoE	Eosinophilic esophagitis
80	FPQ	Food propensity questionnaire
81	HEI	Healthy Eating Index
82	HEI-P	Healthy Eating Index for Pregnancy
83	IgE	Immunoglobulin E
84	OR	Odds ratio
85	ROC	Receiver operating curve

86

87 **Background**

88 The developmental origins of health and disease hypothesis¹ suggests that maternal exposures during
 89 pregnancy, including nutritional intake, may have a significant impact on offspring risk of non-
 90 communicable diseases throughout life. A recent European Academy of Allergy and Clinical
 91 Immunology (EAACI) systematic review² with meta-analysis summarized studies investigating the
 92 association between food patterns and intake of single foods and nutrients during pregnancy on the
 93 development of offspring allergic rhinitis, atopic dermatitis, asthma, wheeze and food allergy. The
 94 review included studies focusing on all aspects of dietary intake. Overall the review showed only one
 95 significant association: a reduction in offspring asthma following maternal vitamin D supplementation
 96 in pregnancy.³⁻⁵

97

98 Single nutrients or foods during pregnancy may show some association with offspring allergy
 99 outcomes. However, nutrients and foods are not eaten in isolation. The 2020-2025 Dietary Guidelines
 100 for Americans state that dietary patterns may better predict overall health status and disease risk than
 101 individual foods or nutrients.⁶ To increase our understanding of the complex relationship between
 102 nutrients and other essential components of food, there has been a growing interest in taking a whole

103 diet approach when studying disease outcomes. The purpose of diet indices is to synthesize a large
104 amount of dietary information into a single useful diet quality indicator.^{7,8} Using diet indices may also
105 increase the feasibility of translating food intake into daily food consumption.

106
107 However, the EAACI review² showed limited associations between any diet pattern or diet index
108 during pregnancy and offspring allergy outcomes. Indices studied included the Healthy Eating Index
109 (HEI),⁹⁻¹¹ the dietary inflammatory index (DII)^{11,12} and the Mediterranean diet score.^{9,13-17}
110 Investigators examined a range of allergy outcomes including wheeze,^{9,11-15,17} asthma,^{9,11,12} rhinitis,
111 atopic dermatitis and/or eczema,¹³⁻¹⁶ sensitisation to food/aero-allergens^{9,10,15} and a combination of
112 allergic diseases.¹⁰ Only one of the six studies focusing on the Mediterranean diet score showed an
113 association with reduced offspring prevalence of persistent wheeze, atopic wheeze and atopy,¹⁵ and no
114 other allergy outcomes studied showed a significant association. One recent study showed an
115 association between maternal energy-adjusted dietary inflammatory index (E-DII)¹¹ scores during
116 pregnancy and offspring asthma outcomes over 10 years. Another study found an association between
117 maternal DII scores¹² and offspring wheeze trajectories, but not asthma, up to 7.5 years of age. No
118 association was found between the HEI for pregnancy (HEI-P)⁹ or the modified HEI-P¹⁰ and any of the
119 allergy outcomes studied.

120
121 One possible rationale for the lack of clear results is that the indices were developed for reasons other
122 than allergy prevention. The goal of this study was to develop a novel index of maternal diet during
123 pregnancy that would be associated with offspring allergy outcomes.

124

125 **Methods**

126 ***Study participants***

127 Participants were from the Healthy Start study, a prospective cohort that enrolled 1410 women during
128 pregnancy at outpatient prenatal clinics affiliated with the University of Colorado Denver from 2009
129 to 2014. Written, informed consent was obtained before the first research visit. The study was
130 approved by the Colorado Multiple Institutional Review Board. Eligible women had singleton
131 pregnancies, no previous stillbirth, older than 16 years of age at the time of consent, gestational age at

time of baseline research visit of less than 24 weeks, no fetal death, and no birth at <25 weeks of gestation. Women were excluded if they experienced asthma treated with steroid medication, cancer, pre-existing diabetes or psychiatric illness. Participants took part in two in-person visits during pregnancy, at a median of 17 weeks (range: 10–24weeks) and 27 weeks (range: 24–32 weeks) of gestation, in addition to one visit immediately after birth. Methods for the Healthy Start study have been reported in detail previously.¹⁸ Participants who did not consent to offspring medical record review up to age four, or with missing maternal dietary data were excluded from this analysis.

139

140 ***Maternal pregnancy diet assessment***

Data regarding maternal diet during pregnancy was obtained through a validated food propensity questionnaire (FPQ).¹⁹The FPQ used was previously validated using dietary intake collected by four 24-hour recalls and a food frequency questionnaire (n=965) to compare against data collected by the FPQ.¹⁹No further validation was carried out in Healthy Start. The FPQ consisted of questions about the intake of 41 food and beverage items. The full FPQ appears in the online supplementary material (S1). Women were asked to complete FPQs at both their mid-pregnancy and delivery research visits. Each FPQ asked women to think back about their diet over the past three months. The data from the two FPQs were combined by computing the maximum of the two responses. This enabled us to take change in food intake over the course of pregnancy into account.²⁰Energy intake was derived from 1-8 (median 2) Automated Self-Administered (ASA) 24-hour recalls²¹that were completed throughout pregnancy, including one at enrollment when staff provided initial instruction and technical support.

152

153 ***Electronic medical record search***

Medical record numbers (MRNs) were found by searching the electronic medical records using the child's name and date of birth. The MRNs were recorded by two independent researchers (CV and MBA) and any discrepancies were reviewed and resolved. The final list of MRNs were sent to the electronic medical record search team at Children's Hospital Colorado. The electronic medical records were searched from birth up to four years of age using previously published terms²² for atopic dermatitis, asthma, wheeze, allergic rhinitis, and food allergies. For each participant, each time there was a text recognition for one of the allergy related search terms, the corresponding medical record

161 notes were recorded verbatim as a text field, as well as the date of the service. The dataset received
162 from the electronic medical record search team included medical record notes for each participant at
163 different service dates.

164

165 ***Child allergy outcomes***

166 Medical records up to age four were assessed for every child in the analytical cohort whose parents
167 had given written informed consent for medical record review. Children were categorized as having
168 no allergy, or a diagnosis of one or more allergic diseases, including allergic rhinitis, atopic dermatitis,
169 asthma, food allergy, or wheeze. A combined allergy outcome, referred to as “any allergy excluding
170 wheeze” was defined as any diagnosis of allergic rhinitis, atopic dermatitis, asthma, or food allergy up
171 to age four years.

172

173 Any text field identified from the search of the electronic medical records was reviewed by either
174 MBA or CV and discrepancies discussed. Diagnoses for atopic dermatitis, asthma, wheeze, allergic
175 rhinitis, and food allergies, were made after extensive review of medical notes. Children with a
176 diagnosis of atopic dermatitis or eczema were considered to have atopic dermatitis, as the common
177 terms often appear interchangeable in the medical record. Similarly, children with a diagnosis of hay
178 fever or seasonal allergies were considered to have allergic rhinitis, based on the same rationale.

179

180 To differentiate between those with non-immunoglobulin E- (IgE) mediated food allergies and those
181 with IgE-mediated food allergy or food intolerance or sensitivity, a more complicated protocol was
182 followed. Records flagged as having a search term associated with food allergy were reviewed (CV)
183 and coded as a suspected food allergy diagnosis, a suspected food intolerance/sensitivity diagnosis or
184 no diagnosis. Participants who had no hits for any food allergy search term were considered to have
185 no food allergy diagnoses. For any participant with suspected food allergy or food
186 intolerance/sensitivity, the full electronic medical record was individually inspected by CV. The full
187 record included clinic notes, information on allergy testing and medical letters. For each participant,
188 whether the child had a food allergy was recorded, and if so, their age at diagnosis. Children with
189 eosinophilic esophagitis (EoE) or food protein induced enterocolitis (FPIES) were not considered to

190 have IgE-mediated food allergies unless they also had co-existing IgE-mediated food allergies. In this
191 report, only children with IgE-mediated food allergies were considered to have the outcome of food
192 allergy. Any unclear diagnoses were re-reviewed by CV and DF, and diagnosis made by consensus.

193
194 Child's age at diagnosis was calculated using their date of birth and the service date associated with
195 their diagnosis. Children whose medical records were reviewed up to age four, but did not return a hit
196 for any of the search terms were considered to have no allergy or wheeze diagnoses.

197 198 ***Demographic data***

199 Information regarding parity, gestational smoking, maternal history of asthma, age of introduction of
200 solid foods, and antibiotic use at any time during pregnancy were reported by mothers via
201 questionnaires. Child's ethnicity was obtained via parental report. Feeding information reported by
202 mothers at the 18-month postnatal interview was used to compute breastfeeding duration as
203 breastmilk months, a product of breastfeeding duration and intensity.²³ Data on maternal age, mode of
204 delivery, gestational diabetes mellitus, and child's sex were obtained from medical records.

205 206 ***Statistical Analysis***

207 *Split sample approach:* A split-sample approach was used to determine replicability.^{24,25} A hybrid
208 1998/2002 32-bit Mersenne twister random number generator was used to assign children with
209 probability of 0.5 to a test set or a replication set.²⁶

210 *Demographic characteristics:* Demographic characteristics were described as frequency and percent,
211 or as mean and standard deviations. Differences between the test and replication subsets were
212 assessed with Pearson chi-square tests for categorical variables, and with t-tests or Wilcoxon rank
213 sum tests for normally or non-normally distributed continuous variables, respectively.

214 *Cumulative incidence:* Cumulative incidence for each diagnosis was calculated as the number of
215 children with the specific diagnosis at any time up to age four, divided by the total number of children
216 with follow-up to age four (i.e., the entire analytic sample size).

217 *Agnostic index development:* Forty-one separate univariable logistic regression models were fit to
218 assess the association of each FPQ item with the outcome of "any allergy excluding wheeze."

219 Assuming a dose-response association, frequency of intake was treated as a continuous variable.
220 A multivariable logistic regression model was fit with the outcome of “any allergy excluding
221 wheeze.” As predictors, the model included any FPQ item which had achieved significance at
222 $\alpha=0.05$ level in the univariable models. FPQ items associated with increased odds were transformed
223 before entry into the multivariable model, so that all items in the model were associated with
224 decreased odds. An agnostic approach was used to assess and remove predictors, until every term in
225 the model was significant at the 0.05 level. The model yielded a weighted combination of predictors.
226 The maternal diet index was defined as the weighted combination of predictors from the model, and
227 scaled to range from 0 to 100.
228 *Replicability analysis:* In the replication set, a logistic model was fit with “any allergy excluding
229 wheeze” as the outcome, and the maternal diet index as the predictor. A chi-squared test compared the
230 areas under the receiver operating characteristic curves for the test and replication set.²⁷
231 *Identification of covariates:* A literature review² identified a set of covariates used in previous
232 publications seeking to identify association between maternal diet during pregnancy and offspring
233 allergy outcomes. The set of covariates identified appear in the online supplementary material (S2). A
234 subset of the covariates was chosen⁹⁻¹⁷ from this larger set based on a directed acyclic graph. Covariate
235 adjusted models included child’s ethnicity, child’s sex, gestational smoking, nulliparity, mode of
236 delivery, maternal history of asthma, breastfeeding duration, age of introduction of solid foods, and
237 energy intake during pregnancy. Two sensitivity analyses were performed. The first included
238 gestational diabetes mellitus as an additional covariate and the second included self-reported maternal
239 antibiotic use during pregnancy as an additional covariate.
240 *Association between index and allergy outcomes:* In the full sample, separate unadjusted and covariate
241 adjusted logistic regression models were fit for each outcome.

243 **Results**

244 *Demographics*

245 Table 1 shows demographic characteristics of the study participants for the full analyticsample
246 (N=1253), the test set (N=606) and the replication set (N=647). Details of participant exclusion and
247 data availability for the analytic sample are presented in a diagram in the online supplementary

248 material (S3).

249

250 *Cumulative incidence of allergic diseases*

251 Table 2 gives the cumulative incidence of each allergic disease, and of the diagnosis “any allergy
252 excluding wheeze.” The percentage of participants ever diagnosed with “any allergy excluding
253 wheeze” was 33% in both the test(200/606)andreplication set (215/647). The disease outcome with
254 the highest cumulative incidence up to four years of age was atopic dermatitis, at 26%. The disease
255 outcome with the lowest cumulative incidence was food allergy, at 3%.

256

257 *Maternal diet during pregnancy*

258 Table 3 summarizes maternal dietary intake during the course of pregnancy. The seven foods most
259 often reported as “never eaten” included liquor(98% reported never eaten), beer(92%), raw fish(88%),
260 wine(83%), tofu/soy-meat substitutes (73%), artificial sweeteners added to coffee and tea (71%), and
261 fish sticks or fried fish/seafood (58%). The seven foods reported most often eaten were fruit(68%
262 reported eating ≥ 1 times per day), milk (61%), bread(54%), cheese (48%), vegetables (44%), 100%
263 pure fruit juice(34%), and cold cereal (32%).

264

265 *Maternal diet index*

266 Seven of the 41 FPQ items emerged as independent predictors of “any allergy excluding wheeze” in
267 the multivariable logistic regression model, and were included in the index: vegetables, yogurt,French
268 fries/fried potatoes, rice/grains, red meats, 100% pure fruit juice and cold cereal. Increased intake of
269 vegetables and yogurt were associated with reduced odds of the diagnosis “any allergy excluding
270 wheeze.” The other items were associated with increased odds of the diagnosis. The multivariable
271 logistic regression model that identified the seven items to be included in the index was fit in the test
272 set, and the beta estimates from this model were used as weights to compute the maternal diet index
273 (Table 4).The index wasscaled to range between 0 and 100, with higher scores associated with better
274 allergy prevention. The equations used to compute the maternal diet index from the weights and scale
275 the index to range between 0 and 100 appear in the online supplementary material (S4). The mean $\pm$
276 SD maternal index in the overall sample was 72.0 ± 1.7 . The distribution of the maternal diet index

for the overall sample is shown in the online supplementary material (S5). Code, and example input and output files are provided in the online supplementary material (S6), and are available for free download from <https://github.com/CarinaVenter/MaternalDietIndex>. The code allows a researcher to compute the maternal diet index using either SAS (SAS Institute, Cary NC) or R²⁸ statistical software.

Figure 1 displays the receiver operating characteristic (ROC) curves, areas under the curves (AUC), and 95% confidence intervals in the test and replication sets. The outcome was the cumulative incidence up to four years of the combined diagnosis of “any allergy excluding wheeze.” The predictor was the maternal diet index. There was no significant difference between the test and replication sets (test set: AUC = 0.70, 95% CI = 0.66-0.75; replication set: AUC = 0.65, 95% CI = 0.61-0.70; $\chi^2 = 2.28$; df = 1; p = 0.13). This result provides support that the association between the index and the outcome replicates.

In unadjusted analyses, increases in the maternal diet index were significantly associated with reduced odds of “any allergy excluding wheeze” in offspring by age four years in both the test set (N = 606, OR = 0.63, 95% CI = 0.56-0.70, p < 0.001) and replication set (N = 647, OR = 0.73, 95% CI = 0.66-0.81, p < 0.001). When adjusting for covariates, increases in the maternal diet index remained significantly associated with reduced odds of “any allergy excluding wheeze” in both the test set (N = 466, OR = 0.74, 95% CI = 0.64-0.87, p < 0.001) and replication set (N = 483, OR = 0.82, 95% CI = 0.70-0.95, p = 0.008).

In separate unadjusted models fit in the full analytic sample (N = 1253), increases in the maternal diet index were significantly associated with reduced odds of offspring diagnosis by age four years of allergic rhinitis (OR = 0.74, 95% CI = 0.67-0.81, p < 0.001), atopic dermatitis (OR = 0.73, 95% CI = 0.67-0.79, p < 0.001), asthma (OR = 0.76, 95% CI = 0.70-0.83, p < 0.001), and wheeze (OR = 0.72, 95% CI = 0.66-0.78, p < 0.001). When adjusting for covariates (N = 949), increases in the maternal diet index remained significantly associated with reduced odds of offspring allergic rhinitis, atopic dermatitis, asthma, and wheeze (Figure 2). There was no significant association between the maternal diet index and offspring odds of food allergy diagnosis by age four years in either the unadjusted (OR

306 = 0.93, 95% CI = 0.78-1.11, $p = 0.44$) or adjusted model (Figure 2), a finding perhaps driven by the
307 low cumulative incidence of food allergy (40/1253). In the sensitivity analyses that included either
308 gestational diabetes mellitus or maternal antibiotic use during pregnancy as an additional covariate,
309 the estimates of association between the diet index and each of the allergy outcomes did not
310 substantially change (data not shown).

311

312 Discussion

313 This study developed an index of maternal diet during pregnancy that was associated with reduced
314 odds of a combined offspring diagnosis of “any allergy excluding wheeze” in a pre-birth cohort of
315 >1200 mother-offspring dyads. The results were replicated using a split sample approach. The
316 index was associated with individual diagnoses of allergic rhinitis, atopic dermatitis, asthma, and
317 wheeze by age four years. This is the first study that has shown associations between an index of
318 maternal dietary intake during pregnancy and multiple offspring allergic diseases.

319

320 The data-derived index included the frequency of consuming vegetables, yogurt, French fries/fried
321 potatoes, rice/grains, red meats, 100% pure fruit juice and cold cereal. This novel index was developed
322 specifically to provide a measure of an allergy-preventative diet in pregnancy. Other studies used
323 indices developed to assess healthy eating, inflammatory diet, or cardiovascular preventive diets,
324 which perhaps explains their limited associations with childhood allergy outcomes. Although nine
325 studies⁹⁻¹⁷ investigated the role of the HEI,⁹⁻¹¹ the DII,^{11,12} and the Mediterranean diet score^{9,13-17} in
326 pregnancy on offspring allergy outcomes, only three studies identified significant associations. These
327 three studies used the Mediterranean diet index¹⁵ and maternal E-DII^{11,12} scores and primarily showed
328 reduction in wheeze or asthma outcomes. No association was found between the HEI-P⁹ or the
329 modified HEI-P¹⁰ and any allergic outcomes.

330 The maternal diet index included items associated with protective and deleterious effects on offspring
331 allergy. Vegetables and yogurt were associated with protective effects, and French fries/fried
332 potatoes, rice/grains, red meats, 100% pure fruit juice and cold cereal were associated with deleterious
333 ones.

334

335 Although an agnostic approach was used to derive and replicate the index, there is a biologically
336 plausible association between maternal diet during pregnancy, and offspring allergy outcomes. Many
337 of the foods in the index are associated with improved or reduced gut microbiome diversity and
338 function. Maternal diet may affect infant microbiome either directly²⁹ or indirectly via the maternal
339 microbiome.³⁰ It is also known that the offspring gut microbiome is associated with a range of
340 offspring allergy outcomes.³¹⁻³³

341
342 Higher vegetable and yogurt intake has been reported to increase gut microbiome diversity. A recent
343 paper by Asnicar et al.³⁴ indicated increased species-level partial correlations upon consumption of
344 vegetables and dairy products (including yogurt). In addition, higher vegetable and yogurt intake in
345 early life was associated with higher levels of fecal butyrate, which in turn was associated with
346 protection from allergy development up to school age.³⁵ Butyrate promotes development of regulatory
347 cells and via epigenetic modifications can also influence immune development *in utero*.^{36,37} While
348 butyrate levels were not measured in this study, future studies will determine if this short-chain fatty
349 acid might mediate the protective effects of maternal yogurt and vegetable consumption on the unborn
350 infant's immune system. On the other hand, intake of foods high in advanced glycosylated end
351 products, such as fried foods, red meat, and fruit juice, all have been associated with lack of gut
352 microbiome diversity in murine models, which might minimize the production of protective
353 metabolites by the maternal microbiome.³⁸

354
355 The findings that maternal intake of cold cereals and rice/grains were associated with increased odds
356 of offspring allergy were initially somewhat unexpected. Cereals, rice and grains usually provide
357 dietary fiber. Dietary fibers, such as the hemi-cellulose fiber arabinoxylan,³⁹ are known to also be
358 substrates for butyrate production in the gut,^{40,41} which should have protective effects as described
359 above. However, intake of cereal, rice and grain probably did not improve fiber intake in this
360 population. For pregnant women in Healthy Start, rice/grains intake included white, sweet and fried
361 rice, which are low in fiber, and cold cereals included low fiber/high sugar cereal. In general, in
362 America, pregnant women eat less fiber than recommended, eating only 1 ounce of whole grains as
363 opposed to the recommended 3-5 ounces.⁶

364

365 In addition to the biological plausibility of the index via the relationship with the gut microbiome, it is
366 reassuring that the maternal diet index aligns with current dietary guidelines. Higher vegetable intake
367 during pregnancy was associated with reduced odds of offspring allergy, while higher red meat intake
368 was associated with increased odds of offspring allergy. These results suggest that pregnant women
369 might want to eat a diet higher in vegetables and lower in red meat. This suggestion would be in line
370 with recommendations from both American and European dietary guidelines. The 2020 – 2025
371 Dietary Guidelines for Americans recommend that pregnant women who need around 2200 kcal per
372 day consume 3 portions of vegetables and 6.5 ounces of protein foods, including meat, poultry,
373 seafood and plant protein, of which approximately 3 ounces should be provided by fish, seafoods or
374 plant-based proteins. European guidelines for pregnant women advise intake of at least five servings
375 of fruit and vegetables and only moderate amounts of red meat.⁴²

376

377 The EAACI review² showed conflicting results about maternal intake of fish and fruit. Based on
378 observational studies, fish/fatty fish intake was associated with reduced prevalence of allergic rhinitis
379 in offspring but increased prevalence of atopic dermatitis and sensitization to common
380 allergens. While some observational studies showed that fruit intake was associated with reduced
381 atopic dermatitis⁴³ and asthma⁴⁴, it was also reported to be associated with increased allergic rhinitis⁴⁴
382 and sensitization⁴⁵ to common allergens.

383

384 The conflicting results in the EAACI review² may bear witness to a lack of strong association between
385 maternal intake of fish or fruit and offspring allergic disease. Neither fruit nor fish appear in the
386 index. The study findings show no apparent association between most maternal fish intake and
387 offspring allergy. One possible explanation is that very few women in the cohort ate fish of any sort.
388 One third indicated that they never ate fatty fish, including mackerel, tuna, lake trout, salmon or
389 sardines. About half of women indicated that they never ate baked, boiled or poached other fish
390 during pregnancy. Although almost 70% of women consumed fruit daily, the index did not predict
391 allergy better when fruit was added.

392

393 The study had some limitations. The study did not show association between the maternal diet index
394 and food allergy. Food allergy occurred in only 40, or 3% of children, as opposed to atopic dermatitis,
395 which appeared in 327, or 26% of children. While the apparent lack of association between the index
396 and food allergy could be a true finding, could be due to a lack of power, or both, the low frequency
397 of food allergy implicates lack of power as the most likely factor. Further studies with larger sample
398 sizes of offspring with food allergy will eventually demonstrate whether it was a power issue, or a
399 true null result. Other limitations include that allergy data was abstracted from electronic medical
400 records rather than by objective diagnosis. There are many factors that could have possibly influenced
401 our study outcomes that we did not have data for including antacid, probiotic and infections during
402 pregnancy and early infancy.

403
404 Strengths of the study include assessment of maternal dietary intake at two timepoints, yielding an
405 overall view of maternal diet intake for six months of pregnancy. Healthy Start includes a multi-ethnic
406 population which improves the generalizability of the results. The statistical approach permitted
407 replication of the results. Intensive phenotyping allowed inclusion of a large number of relevant
408 covariates, such as gestational smoking, nulliparity, mode of delivery, maternal history of asthma,
409 maternal energy intake during pregnancy, breastfeeding duration, age of introduction of solid foods,
410 child's ethnicity, and child's sex. The online tool will allow other researchers to easily compute the
411 maternal diet index.

412
413 In summary, this study developed and validated a novel maternal diet index for allergy prevention.
414 Increases in the index were significantly associated with reduced odds of asthma, allergic rhinitis,
415 atopic dermatitis and wheeze, but not food allergy. This is the first maternal diet index which has been
416 associated with multiple offspring allergic diseases. The results give hope for avenues for the
417 prevention of allergic diseases *in utero*. Replication in further cohorts and a randomized controlled
418 clinical trial of a diet intervention for women during pregnancy are needed to verify whether a diet
419 high in yogurt and vegetables, and low in tater tots, fried potatoes, red meat, fruit juice, low fiber
420 grains, and sugar-sweetened cereals in pregnancy can reduce allergy outcomes in offspring.

421

422 **Author contributions**

423 Dr. Venter identified the need to develop a dietary index in pregnancy for allergy prevention, was
424 involved in extraction of the allergy information and lead the manuscript writing. Dr Glueck led the
425 statistical analysis performed by Ms. Palumbo and Dr. Bingham. Dr. O'Mahony assisted with the data
426 interpretation, Dr. Fleischer and Dr. Ben-Abdallah assisted with allergy record extraction and defining
427 the allergy phenotypes. Dr. Sauder assisted with the interpretation of the nutritional analysis. Dr.
428 Dabelea is the principal investigator of the Healthy Start study.

429

430 **Declaration of interest**

431 Dr. Fleischer has received research support from Aimmune Therapeutics and DBV Technologies; has
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Table 1. Demographic characteristics of study participants

	Overall sample	Test subset	Replication subset	
Sample size (N)	1253	606	647	
Continuous variables	← mean ± SD[†] →			p-value[‡]
Energy intake during pregnancy (kcal/day)	2062 ± 384	2079 ± 411	2046 ± 357	0.14
Breastfeeding duration (breastmilk-months)	8.35 ± 6.78	7.93 ± 6.54	8.76 ± 6.98	0.08
Age of introduction of solid foods (months)	6.17 ± 1.98	6.14 ± 1.95	6.19 ± 2.01	0.70
Categorical variables	← n (%) →			p-value[‡]
Gestational smoking	106 (8)	64 (11)	42 (6)	0.01
Nulliparous	594 (47)	285 (47)	309 (48)	0.80
Maternal history of asthma	208 (17)	104 (17)	104 (16)	0.60
Mode of delivery – vaginal	969 (78)	473 (79)	496 (77)	0.46
Child's race/ethnicity				0.06
Non-Hispanic white	630 (50)	300 (50)	330 (51)	
Non-Hispanic Black	160 (13)	69 (11)	91 (14)	
Hispanic	320 (26)	174 (29)	146 (23)	
Other [§]	143 (11)	63 (10)	80 (12)	
Child's sex – female	600 (48)	291 (48)	309 (48)	0.93
Child diagnosis of “any allergy excluding wheeze” [¶]	415 (33)	200 (33)	215 (33)	0.93

[†] SD: Standard deviation

[‡] p-value for hypothesis test comparing demographic variables between those randomized to

the test or replication set. Statistical tests included t-tests for normally distributed continuous variables, Wilcoxon rank sum tests for non-normally distributed continuous variables, and Pearson chi-square tests for categorical variables

§ Other ethnicity includes non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multi-racial.

¶ The combined outcome “any allergy excluding wheeze” was defined as any diagnosis of allergic rhinitis, atopic dermatitis, asthma, and/or food allergy by age four years.

Table 2. Cumulative incidence of electronic medical record verified allergic disease diagnoses in children up to age four years (N=1253)

Allergic disease outcome	n (%)
Allergic rhinitis	137 (11)
Atopic dermatitis	327 (26)
Asthma	182 (15)
Wheeze	232 (19)
Food allergy	40 (3)

Table 3. Summary of Healthy Start participants' reported intake of each food propensity questionnaire item (N=1253)

Food propensity questionnaire item	% participants reporting each level of consumption			
	Never	1-3 times per month	1-6 times per week	≥1 times per day
Fruit including fresh, frozen, or canned	0.4	2.3	28.9	68.4
Bread	0.6	2.1	43.2	54.2
Cheese – any kind	1.0	4.2	46.4	48.4
Vegetables[†]	1.4	5.4	49.6	43.6
Pizza	2.2	51.5	45.3	1.0
Salads	2.2	11.8	68.1	18.0
Cookies, cake, pie, brownies	2.4	28.8	58.9	9.9
Ice cream, frozen yogurt, or sherbet	3.1	19.4	66.7	10.8
Fried potatoes such as French fries, etc. [†]	3.2	31.8	59.6	5.3
Potatoes such as baked, boiled, mashed, sweet	3.7	33.7	58.7	3.9
Rice or other cooked grains[†]	3.7	16.4	68.9	11.1
Cold cereal[†]	3.7	7.8	56.4	32.1
100% pure fruit juice[†]	4.2	16.8	44.7	34.4
Chicken – baked, grilled, sautéed, broiled	4.4	19.6	72.9	3.2
Chocolate or other types of candy	4.6	18.3	57.4	19.6
Milk	5.2	5.2	28.8	60.8
Red meat[†]	6.1	13.6	71.7	8.5
Beans	6.9	33.4	53.9	5.7
Yogurt (not including frozen yogurt) [†]	7.7	15.5	53.7	23.1
Doughnuts, sweet rolls, Hispanic “pan dulce,” etc.	8.1	40.9	44.8	6.3
Processed meat	11.3	30.2	51.0	7.6

Oatmeal, grits, other cooked cereal	17.6	29.4	43.5	9.5
Soft drinks, soda, pop	17.9	21.3	38.9	21.8
Artificial fruit drinks such as Hi-C, Kool-Aid	21.0	24.3	33.8	20.8
Tea – iced or hot, caffeinated or decaffeinated	26.1	18.8	36.0	19.0
Fried chicken including chicken nuggets	26.3	42.4	29.1	2.2
Popcorn	26.3	53.6	18.5	1.6
Sugar or honey added to coffee or tea	33.2	20.5	30.0	16.3
Fatty fish – baked, boiled, poached, grilled, canned	33.3	42.9	23.6	0.2
Dried fruit	34.7	26.7	33.0	5.5
Coffee – caffeinated or decaffeinated	36.2	16.0	25.8	22.0
Smoked fish or seafood, such as lox	45.6	34.7	19.2	0.6
Other fish – baked, boiled, poached, grilled	50.9	35.0	13.8	0.3
Pudding, custard, or flan	52.4	30.1	15.5	2.0
Fish sticks or fried fish, shellfish, or seafood	58.3	33.8	7.3	0.5
Artificial sweetener added to coffee or tea	71.2	10.2	11.7	6.9
Tofu, soy burgers, soy-meat substitutes	72.7	16.6	10.1	0.6
Wine or wine coolers	83.4	15.3	1.2	0.1
Raw fish including ceviche and raw fish in sushi	88.0	10.9	0.9	0.2
Beer	91.8	6.9	1.2	0.1
Liquor or mixed drinks	98.1	1.8	0.1	0.0

† Denotes food propensity questionnaire items that were included in the maternal diet index.

Table 4. Multivariable logistic regression model fit in the test set (N=606) to predict offspring diagnosis by age four years of “any allergy excluding wheeze”[†] and used to derive the maternal diet index

Predictor	Beta estimate	Standard error	p-value
Intercept	33.01	5.10	<0.01
Vegetables [‡]	-0.41	0.16	0.01
Yogurt [‡]	-0.56	0.21	0.01
French fries/fried potatoes [§]	-0.86	0.33	0.01
Rice/grains [§]	-0.58	0.25	0.02
100% pure fruit juice [§]	-0.19	0.08	0.02
Red meats [§]	-0.58	0.28	0.04
Cold cereal [§]	-0.44	0.18	0.02

[†]The combined outcome “any allergy excluding wheeze” was defined as any diagnosis of allergic rhinitis, atopic dermatitis, asthma, and/or food allergy.

[‡] The item was associated with a protective effect on child allergy in the univariable model, and was therefore included as a continuous predictor with units of number of times consumed per day in the multivariable model presented in this table

[§] The item was associated with a harmful effect on child allergy in the univariable model, and was therefore included in the multivariable model presented in this table as a continuous predictor computed as follows: predictor value = 13 – number of times consumed per day

Figure legends:

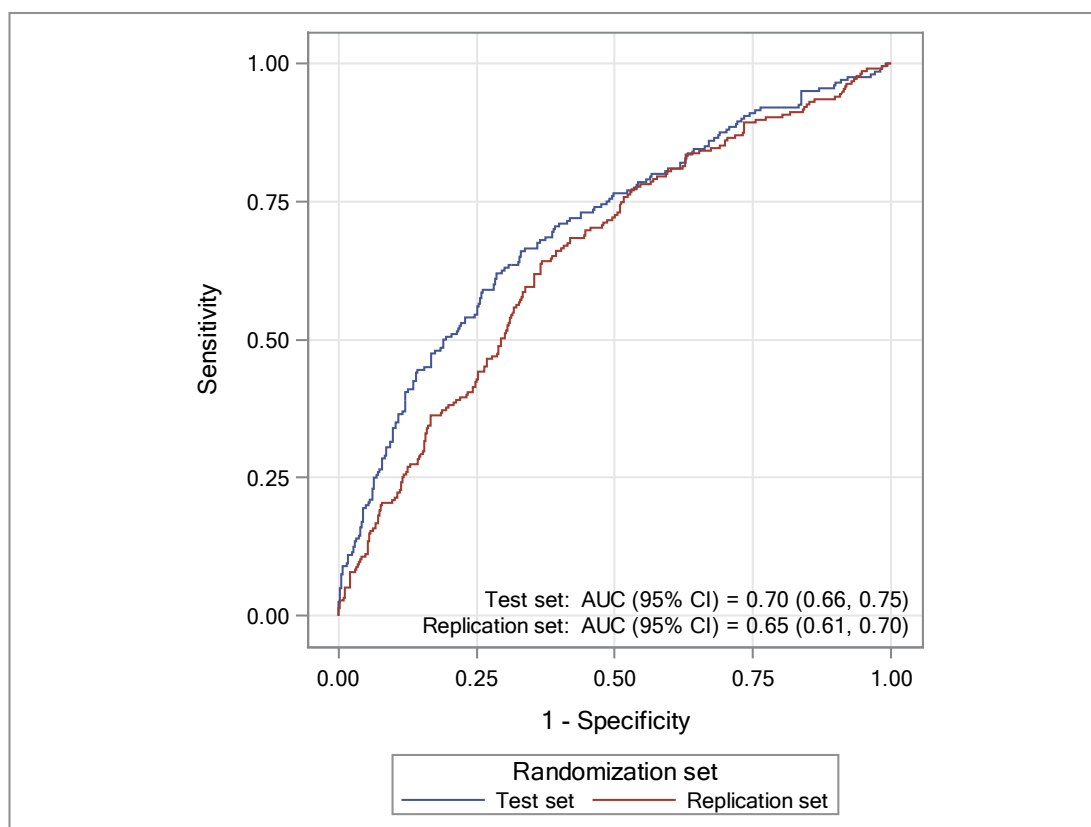


Figure 1. Receiver operating characteristics curves and areas under the curves (AUCs) for the maternal diet index as a predictor of the cumulative incidence by age four years of offspring diagnosis of the combined outcome “any allergy excluding wheeze” in test and replication sets.

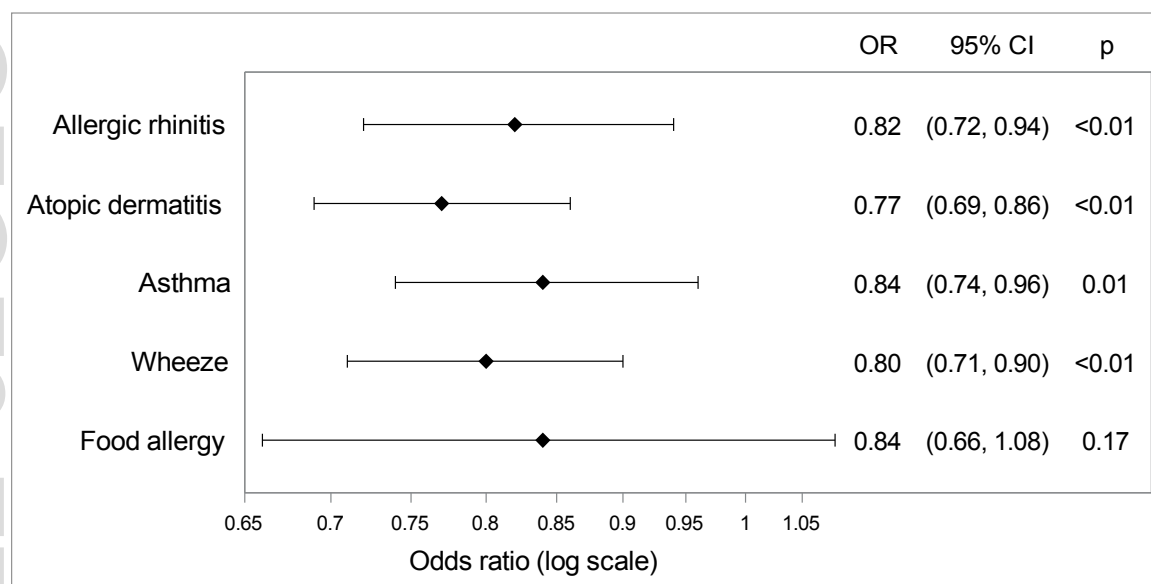


Figure 2. Adjusted associations (N = 949) between the maternal diet index and odds of offspring diagnosis by age four years of allergic outcomes.

Supplementary material: S1. Questions included on the Food Propensity Questionnaire¹ (FPQ) administered to Healthy Start mothers

During the past three months...

1. How often did you drink **100% pure fruit juice** such as orange, mango, apple, grape and pineapple juices? Do not include fruit-flavored drinks with added sugar or fruit juice you made at home and added sugar to.

NEVER ☐			
1 time per month or less ☐		1 time per day ☐	
2-3 times per month ☐		2-3 times per day ☐	
1-2 times per week ☐		4-5 times per day ☐	
3-4 times per week ☐		6 or more times per day ☐	
5-6 times per week ☐			

2. How often did you drink other **fruit drinks** (such as cranberry cocktail, Hi-C, lemonade, or Kool-Aid, diet or regular)?

NEVER ☐			
1 time per month or less ☐		1 time per day ☐	
2-3 times per month ☐		2-3 times per day ☐	
1-2 times per week ☐		4-5 times per day ☐	
3-4 times per week ☐		6 or more times per day ☐	
5-6 times per week ☐			

3. Did you drink **soft drinks, soda, or pop**?

NO ☐ (GO TO QUESTION 4)
 YES ☐

3a. How often did you drink **soft drinks, soda, or pop**?

NEVER ☐			
1 time per month or less ☐		1 time per day ☐	
2-3 times per month ☐		2-3 times per day ☐	
1-2 times per week ☐		4-5 times per day ☐	
3-4 times per week ☐		6 or more times per day ☐	
5-6 times per week ☐			

3b. How often were these fruit drinks, soft drinks, soda, or pop **diet or sugar-free**?

Almost never or never ☐	
About ¼ of the time ☐	
About ½ of the time ☐	
About ¾ of the time ☐	
Almost always or always ☐	

3c. How often were these soft drinks, soda, or pop **caffeine-free**?

Almost never or never ☐	
About ¼ of the time ☐	
About ½ of the time ☐	
About ¾ of the time ☐	
Almost always or always ☐	

4. How often did you have **milk** either to drink or on cereal? Do not include soy milk or small amounts of milk in coffee or tea.

NEVER ☐			
1 time per month or less ☐		1 time per day ☐	
2-3 times per month ☐		2-3 times per day ☐	
1-2 times per week ☐		4-5 times per day ☐	
3-4 times per week ☐		6 or more times per day ☐	
5-6 times per week ☐			

5. How often did you drink **beer**?

NEVER ☐

1 time per month or less ☐
2-3 times per month ☐
1-2 times per week ☐
3-4 times per week ☐
5-6 times per week ☐

1 time per day ☐
2-3 times per day ☐
4-5 times per day ☐
6 or more times per day ☐

6. How often did you drink **wine** or **wine coolers**?

NEVER ☐

1 time per month or less ☐
2-3 times per month ☐
1-2 times per week ☐
3-4 times per week ☐
5-6 times per week ☐

1 time per day ☐
2-3 times per day ☐
4-5 times per day ☐
6 or more times per day ☐

7. How often did you drink **liquor** or **mixed drinks**?

NEVER ☐

1 time per month or less ☐
2-3 times per month ☐
1-2 times per week ☐
3-4 times per week ☐
5-6 times per week ☐

1 time per day ☐
2-3 times per day ☐
4-5 times per day ☐
6 or more times per day ☐

8. How often did you eat **oatmeal**, **grits**, or **other cooked cereal**?

NEVER ☐

1 time per month ☐
2-3 times per month ☐
1 time per week ☐
2 times per week ☐
3-4 times per week ☐

5-6 times per week ☐
1 time per day ☐
2 or more times per day ☐

9. How often did you eat **cold cereal** (box cereal such as Corn Flakes)?

NEVER ☐ (GO TO QUESTION 10)

1 time per month ☐
2-3 times per month ☐
1 time per week ☐
2 times per week ☐
3-4 times per week ☐

5-6 times per week ☐
1 time per day ☐
2 or more times per day ☐

9a. How often was the cold cereal you ate a **whole grain type** (such as shredded wheat, Wheaties, Cheerios, Raisin Bran or other bran, oat, or whole wheat cereal)?

Almost never or never ☐
About $\frac{1}{4}$ of the time ☐
About $\frac{1}{2}$ of the time ☐
About $\frac{3}{4}$ of the time ☐
Almost always or always ☐

10. How often did you eat **dried fruit**, such as prunes or raisins?

NEVER ☐

1 time per month ☐
2-3 times per month ☐
1 time per week ☐
2 times per week ☐
3-4 times per week ☐

5-6 times per week ☐
1 time per day ☐
2 or more times per day ☐

11. How often did you eat **fruit**? Include **fresh, frozen** or **canned fruit**. Do not include juices or dried.

NEVER ☐

1 time per month or less ☐
2-3 times per month ☐
1-2 times per week ☐
3-4 times per week ☐
5-6 times per week ☐

1 time per day ☐
2-3 times per day ☐
4-5 times per day ☐
6 or more times per day ☐

12. How often did you eat **lettuce salads, including spinach** (with or without other vegetables)?

NEVER ☐

1 time per month ☐
2-3 times per month ☐
1 time per week ☐
2 times per week ☐
3-4 times per week ☐

5-6 times per week ☐
1 time per day ☐
2 or more times per day ☐

13. How often did you eat **French fries, home fries, hash browned potatoes, or tater tots**?

NEVER ☐

1 time per month ☐
2-3 times per month ☐
1 time per week ☐
2 times per week ☐
3-4 times per week ☐

5-6 times per week ☐
1 time per day ☐
2 or more times per day ☐

14. How often did you eat any other **kind of potatoes**, such as baked, boiled, mashed potatoes, sweet potatoes, or potato salad?

NEVER ☐

1 time per month ☐
2-3 times per month ☐
1 time per week ☐
2 times per week ☐
3-4 times per week ☐

5-6 times per week ☐
1 time per day ☐
2 or more times per day ☐

15. How often did you eat **cooked dried beans**, such as refried beans, baked beans, beans in soup, pork and beans or any other type?

NEVER ☐

1 time per month ☐
2-3 times per month ☐
1 time per week ☐
2 times per week ☐
3-4 times per week ☐

5-6 times per week ☐
1 time per day ☐
2 or more times per day ☐

16. How often did you eat **other vegetables**, not including what you just told me about (lettuce salads, potatoes, or cooked dried beans)?

NEVER ☐

1 time per month ☐
2-3 times per month ☐
1 time per week ☐
2 times per week ☐
3-4 times per week ☐

5-6 times per week ☐
1 time per day ☐
2 or more times per day ☐

17. How often did you eat **rice** or **other cooked grains** (such as bulgur, cracked wheat, or millet)?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

18. How often did you eat **bread** including toast, rolls and sandwiches?

NEVER ☐ (GO TO QUESTION 19)

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 -3 times per day ☐

4-5 times per day ☐

6 or more times per day ☐

18a. How often was the bread you ate **whole grain bread** (this includes whole wheat, rye, oatmeal and pumpernickel)?

Almost never or never ☐

About $\frac{1}{4}$ of the time ☐

About $\frac{1}{2}$ of the time ☐

About $\frac{3}{4}$ of the time ☐

Almost always or always ☐

19. How often did you eat **processed meat**, such as bacon, lunch meats, or hot dogs?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

20. How often did you eat **red meat**, such as beef, pork, ham, or sausage? Do not include chicken, turkey or seafood.

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

21. How often did you eat **fried chicken** (including chicken nuggets)?

NEVER ☐ (GO TO QUESTION 22)

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

21a. How often did you eat chicken **WITH skin**?

NONE ☐

Almost never or never ☐

About $\frac{1}{4}$ of the time ☐

About $\frac{1}{2}$ of the time ☐

About $\frac{3}{4}$ of the time ☐

Almost always or always ☐

22. How often did you eat **chicken** that was either **baked, grilled, sautéed, or broiled** (not fried)?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

23. How often did you eat **smoked fish** or **seafood** (such as smoked salmon, lox, or others)?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

24. How often did you eat **raw fish**, including ceviche and raw fish in sushi?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

25. How often did you eat **fish sticks** or **fried fish** (including fried **seafood** or **shellfish**)?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

26. How often did you eat **fish** or **seafood** that was either **baked, broiled, poached, or grilled**, or **canned specifically - mackerel, tuna, lake trout, herring, salmon or sardines**?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

27. How often did you eat any **other type of fish** that was **baked, broiled, poached, or grilled**?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

28. How often did you eat **tofu, soy burgers, or soy meat-substitutes**?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

29. How often did you eat **pizza**? Include frozen pizza, fast food pizza, and homemade pizza.

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

30. How often did you eat **popcorn** (including low-fat)?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

31. How often did you eat **yogurt** (NOT including frozen yogurt)?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

32. How often did you eat any kind of **cheese**? Include cheese as a snack, cheese on burgers, sandwiches, and cheese in foods such as lasagna, quesadillas, or casseroles. (Please do not count cheese on pizza).

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

33. How often did you eat **ice cream, ice cream bars, frozen yogurt or sherbet** (including low-fat or fat-free)? Do not include sugar free.

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

34. How often did you eat **pudding, custard or flan**?

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

35. How often did you eat **doughnuts, sweet rolls, danishes, Hispanic “pan dulce,” pop-tarts or muffins**? Do not include sugar free items.

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2-3 times per day ☐

4-5 times per day ☐

6 or more times per day ☐

36. How often did you eat **cookies, cake, pie or brownies**? Do not include sugar-free kinds.

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2-3 times per day ☐

4-5 times per day ☐

6 or more times per day ☐

37. How often did you eat **chocolate** or any other types of **candy**? Do not include sugar-free candy.

NEVER ☐

1 time per month ☐

2-3 times per month ☐

1 time per week ☐

2 times per week ☐

3-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2 or more times per day ☐

38. How many cups of **coffee**, caffeinated or decaffeinated, did you drink?

NONE ☐ (GO TO QUESTION 39)

Less than 1 cup per month ☐

1-3 cups per month ☐

1 cup per week ☐

2-4 cups per week ☐

5-6 cups per week ☐

1 cup per day ☐

2-3 cups per day ☐

4-5 cups per day ☐

6 or more cups per day ☐

38a. How often was the coffee you drank **decaffeinated**?

Almost never or never ☐

About $\frac{1}{4}$ of the time ☐

About $\frac{1}{2}$ of the time ☐

About $\frac{3}{4}$ of the time ☐

Almost always or always ☐

39. How many glasses of **iced or hot tea**, caffeinated or decaffeinated, did you drink?

NONE ☐ (GO TO QUESTION 40)

Less than 1 cup per month ☐

1-3 cups per month ☐

1 cup per week ☐

2-4 cups per week ☐

5-6 cups per week ☐

1 cup per day ☐

2-3 cups per day ☐

4-5 cups per day ☐

6 or more cups per day ☐

39a. How often was the iced or hot tea you drank **decaffeinated** or **herbal tea**?

Almost never or never ☐

About $\frac{1}{4}$ of the time ☐

About $\frac{1}{2}$ of the time ☐

About $\frac{3}{4}$ of the time ☐

Almost always or always ☐

40. How often did you drink coffee or tea that had **sugar** or **honey** added to it? Include coffee and tea you sweetened yourself and presweetened tea and coffee drinks such as *Arizona Iced Tea* and *Frappuccino*. Do not include artificially sweetened coffee or diet tea.

NEVER ☐

Less than 1 time per month ☐

1-3 times per month ☐

1 time per week ☐

2-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2-3 times per day ☐

4-5 times per day ☐

6 or more times per day ☐

41. How often did you add **artificial sweetener** to your coffee or tea?

NEVER ☐

Less than 1 time per month ☐

1-3 times per month ☐

1 time per week ☐

2-4 times per week ☐

5-6 times per week ☐

1 time per day ☐

2-3 times per day ☐

4-5 times per day ☐

6 or more times per day ☐

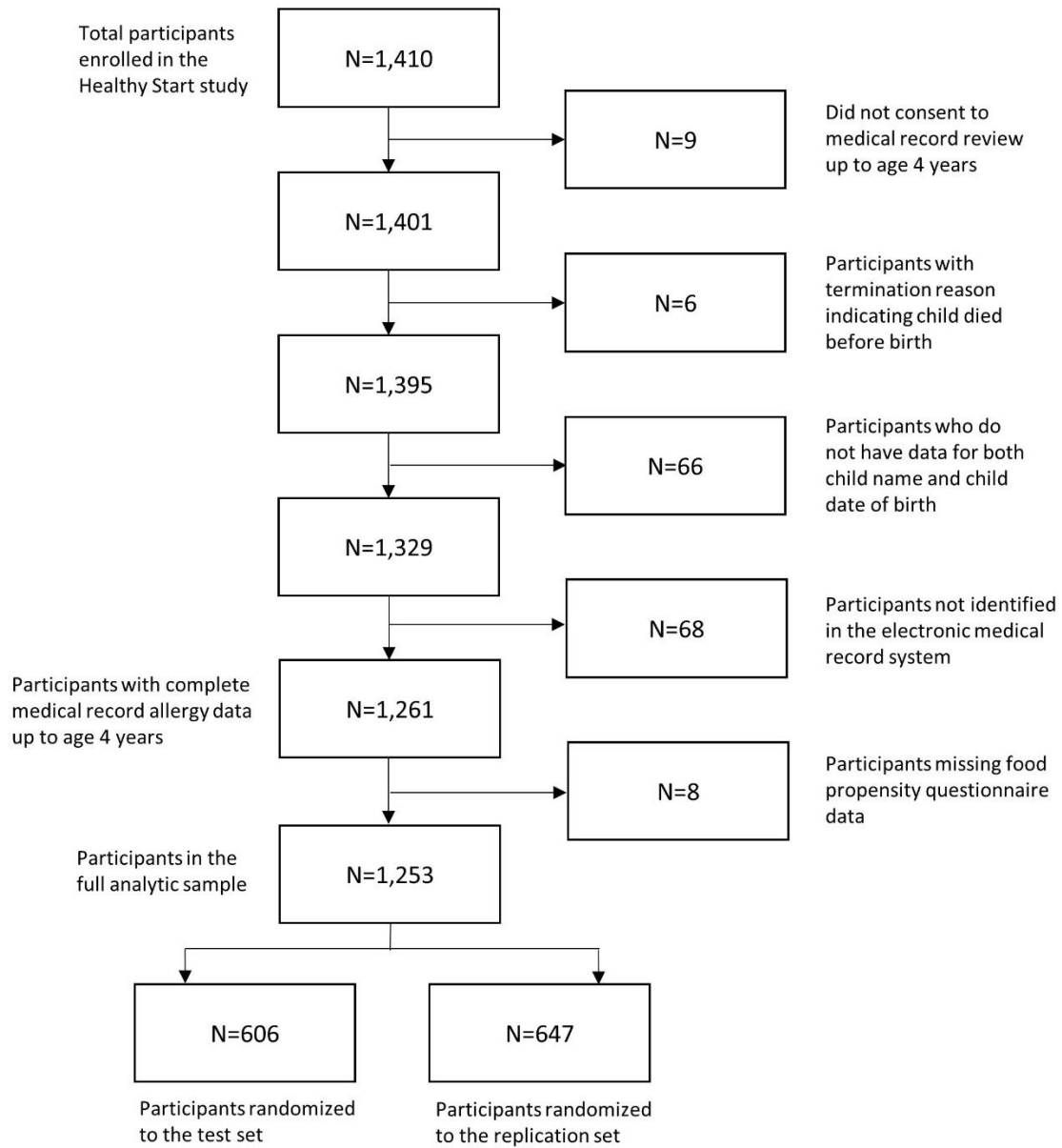
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[illegible]

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Supplementary material: S3. Diagram of participant exclusion leading to the analytic sample.



Supplementary material: S4. Computation of maternal diet index.

The equation below (Eq. 1) gives the equation for the computing the raw (unscaled) maternal diet index as the linear predictor of the final model:

$$\begin{aligned} \text{Raw index} = & 33.01 + (-0.41) * \text{DailyVeg} \\ & + (-0.56) * \text{DailyYogurt} \\ & + (-0.86) * (13 - \text{DailyFriesTots}) \\ & + (-0.58) * (13 - \text{DailyRiceGrains}) \\ & + (-0.19) * (13 - \text{DailyPureFrJuice}) \\ & + (-0.58) * (13 - \text{DailyRedMeat}) \\ & + (-0.44) * (13 - \text{DailyColdCereal}) \end{aligned} \quad (\text{Eq. 1})$$

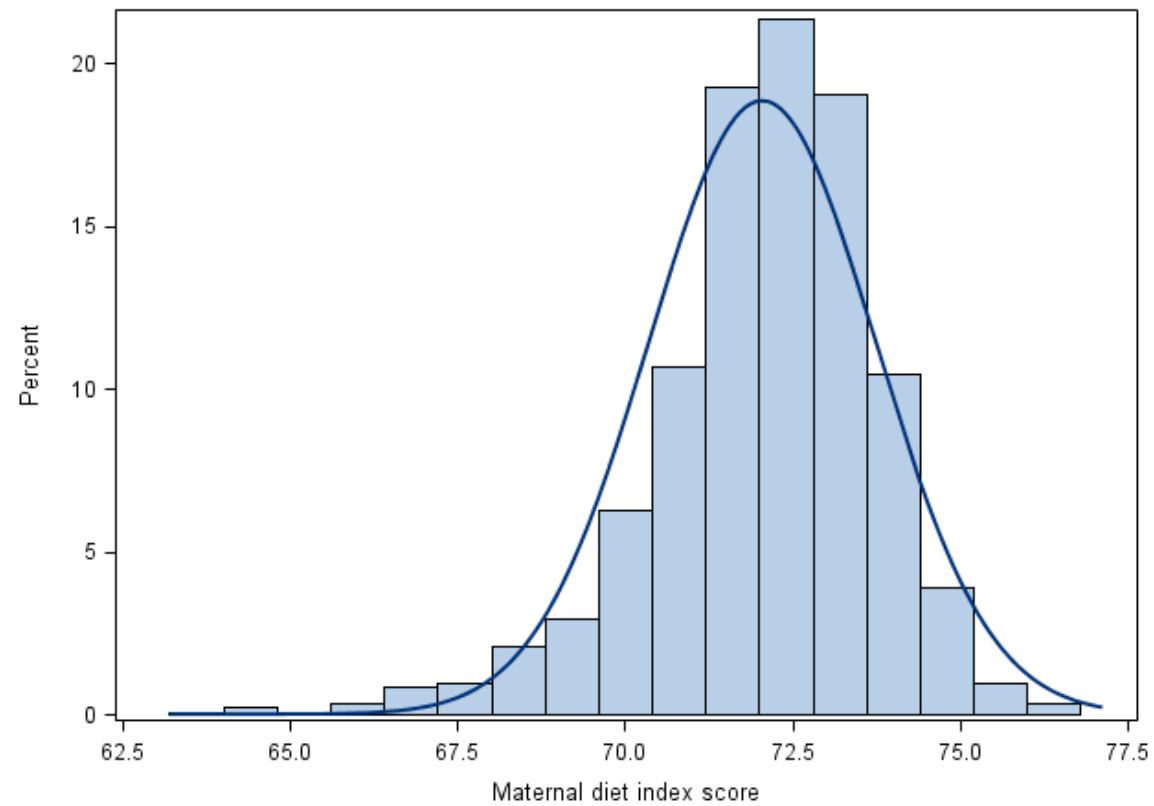
The variables in Equation 1 can be defined as follows:

- DailyVeg: The number of times per day a person reported to consume vegetables
- DailyYogurt: The number of times per day a person reported to consume yogurt
- DailyFriesTots: The number of times per day a person reported to consume French fries, tater tots, other fried potatoes, etc.
- DailyRiceGrains: The number of times per day a person reported to consume rice and other cooked grains
- DailyPureFrJuice: The number of times per day a person reported to consume 100% pure fruit juice
- DailyRedMeat: The number of times per day a person reported to consume red meat
- DailyColdCereal: The number of times per day a person reported to consume cold cereal

The raw (unscaled) maternal diet index is scaled according to Equation 2 to compute the final, scaled maternal diet index, using the theoretical minimum raw diet index score (-13.90) and the theoretical maximum raw diet index score (33.01).

$$\text{Scaled maternal diet index} = \frac{100 * (\text{Raw index} - 33.01)}{(-13.90 - 33.01)} \quad (\text{Eq. 2})$$

Supplementary material: S5. Distribution of maternal diet index in the overall sample (N=1253).



Supplementary material: S6. Resources for computing the maternal diet index in SAS (SAS Institute, Cary NC) and R¹ statistical programming languages.

Computing maternal diet index in R:

Code for R function to compute maternal diet index:

```
ComputeDietIndex <- function(VegLab, YogLab, FriesLab, RiceLab, JuiceLab, RedMeatLab, CerealLab,
Units) {
```

```
  # Create temporary data.frame object with all input variables (except Units) as columns
```

```
  temp <- data.frame(VegLab, YogLab, FriesLab, RiceLab, JuiceLab, RedMeatLab, CerealLab)
```

```
  # Convert units to number of times per day if they are not already
```

```
  if (Units=="Days") {
```

```
    temp <- temp
```

```
  } else if (Units=="Weeks") {
```

```
    temp <- data.frame(apply(temp, 2, function(x) x*(52/365)))
```

```
  } else if (Units=="Months"){
```

```
    temp <- data.frame(apply(temp, 2, function(x) x*(12/365)))
```

```
  } else {
```

```
    stop("Invalid input for argument Units")
```

```
}
```

```
  # Cap maximum daily consumption at 13 times per day
```

```
  temp$VegLab <- pmin(temp$VegLab, 13)
```

```
  temp$YogLab <- pmin(temp$YogLab, 13)
```

```
  temp$FriesLab <- pmin(temp$FriesLab, 13)
```

```
  temp$RiceLab <- pmin(temp$RiceLab, 13)
```

```
  temp$JuiceLab <- pmin(temp$JuiceLab, 13)
```

```
  temp$RedMeatLab <- pmin(temp$RedMeatLab, 13)
```

```
  temp$CerealLab <- pmin(temp$CerealLab, 13)
```

```
  # Compute raw index score
```

```
  RawScores <- 33.0108 + (-0.4106*temp$VegLab) + (-0.5590*temp$YogLab) + (-0.8566*(13-
temp$FriesLab)) + (-0.5752*(13-temp$RiceLab)) + (-0.1870*(13-temp$JuiceLab)) + (-0.5793*(13-
temp$RedMeatLab)) + (-0.4406*(13-temp$CerealLab))
```

```

# Compute min raw index score

MinRaw <- 33.0108 + (-0.4106*13) + (-0.5590*13) + (-0.8566*(13-0)) + (-0.5752*(13-0)) + (-0.1870*(13-0)) + (-0.5793*(13-0)) + (-0.4406*(13-0))

# Compute max raw index score

MaxRaw <- 33.0108 + (-0.4106*0) + (-0.5590*0) + (-0.8566*(13-13)) + (-0.5752*(13-13)) + (-0.1870*(13-13)) + (-0.5793*(13-13)) + (-0.4406*(13-13))

# Compute scaled index score

IndexScore <- (100*(RawScores - MaxRaw))/(MinRaw - MaxRaw)

# Return the index score

return(IndexScore)

}

```

Example R code for utilizing function to compute maternal diet index scores given example input dataset or example input values:

```

load(file="ExampleData.Rdata")

ExampleData

# Compute index scores for example dataset

ComputeDietIndex(VegLab = ExampleData$Veg, YogLab = ExampleData$Yog, FriesLab =
ExampleData$Fries, RiceLab = ExampleData$Rice, JuiceLab = ExampleData$Juice, RedMeatLab =
ExampleData$Meat, CerealLab = ExampleData$Cereal, Units="Weeks")

# Add index score as variable to example dataset

ExampleData$IndexScore <- ComputeDietIndex(VegLab = ExampleData$Veg, YogLab =
ExampleData$Yog, FriesLab = ExampleData$Fries, RiceLab = ExampleData$Rice, JuiceLab =
ExampleData$Juice, RedMeatLab = ExampleData$Meat, CerealLab = ExampleData$Cereal,
Units="Weeks")

ExampleData

# Can use the function to compute a single index score by providing single numeric inputs as follows:

ComputeDietIndex(VegLab = 3, YogLab = 1, FriesLab = 0.5, RiceLab = 0.2, JuiceLab = 1, RedMeatLab = 0,
CerealLab = 1, Units="Days")

```

Example output from running example R code:

```
> ## Load in example dataset
> load(file="ExampleData.Rdata")
> ExampleData
  PID Veg Yog Fries Rice Juice Meat Cereal
1 001 21 5 7 4 7 2 5
2 002 5 3 10 7 14 5 10
3 003 15 7 2 10 5 0 2
4 004 25 10 0 5 0 3 0
5 005 18 6 5 2 1 7 7
6 006 7 4 3 6 3 1 4
7 007 30 8 1 8 10 6 14
8 008 11 2 6 0 4 4 3
9 009 13 0 12 6 8 11 1
10 010 18 1 4 3 6 5 5
> # Compute index scores for example dataset
> ComputeDietIndex(VegLab = ExampleData$Veg, YogLab = ExampleData$Yog, FriesLab = ExampleData$Fries,
+ RiceLab = ExampleData$Rice, JuiceLab = ExampleData$Juice, RedMeatLab = ExampleData$Meat,
+ CerealLab = ExampleData$Cereal, Units="Weeks")
[1] 72.65786 67.42399 73.36874 76.54270 72.51667 71.97041 73.07322 71.94657 68.05614 72.08880
> # Add index score as variable to example dataset
> ExampleData$IndexScore <- ComputeDietIndex(VegLab = ExampleData$Veg, YogLab = ExampleData$Yog, FriesLab = ExampleData$Fries,
+ RiceLab = ExampleData$Rice, JuiceLab = ExampleData$Juice, RedMeatLab = ExampleData$Meat,
+ CerealLab = ExampleData$Cereal, Units="Weeks")
> ExampleData
  PID Veg Yog Fries Rice Juice Meat Cereal IndexScore
1 001 21 5 7 4 7 2 5 72.65786
2 002 5 3 10 7 14 5 10 67.42399
3 003 15 7 2 10 5 0 2 73.36874
4 004 25 10 0 5 0 3 0 76.54270
5 005 18 6 5 2 1 7 7 72.51667
6 006 7 4 3 6 3 1 4 71.97041
7 007 30 8 1 8 10 6 14 73.07322
8 008 11 2 6 0 4 4 3 71.94657
9 009 13 0 12 6 8 11 1 68.05614
10 010 18 1 4 3 6 5 5 72.08880
> # Can use the function to compute a single index score by providing single numeric inputs as follows:
> ComputeDietIndex(VegLab = 3, YogLab = 1, FriesLab = 0.5, RiceLab = 0.2, JuiceLab = 1, RedMeatLab = 0, CerealLab = 1, Units="Days")
[1] 74.45006
```

Computing maternal diet index in SAS:

Code for SAS macro to compute maternal diet index scores given an input dataset:

```
%macro ComputeDietIndex(indat=, idLab=, VegLab=, YogLab=, FriesLab=,
RiceLab=, JuiceLab=, RedMeatLab=, CerealLab=, Units=, outdat=);

options nonotes;

/*Convert units to number of times per day if they are not already*/
/*Create intermediate dataset 1.*/
%if &Units. = "Days" %then
    %do;
        data interim1;
            set &indat.;

            /*No conversion needed. Keep the intake frequency
variables the same*/

            &VegLab. = &VegLab.;
            &YogLab. = &YogLab.;
            &FriesLab. = &FriesLab.;
            &RiceLab. = &RiceLab.;
            &JuiceLab. = &JuiceLab.;
            &RedMeatLab. = &RedMeatLab.;
            &CerealLab. = &CerealLab.;

            run;
        %end;
    %else %if &Units. = "Weeks" %then
        %do;
            data interim1;
                set &indat.;
```

```

        /*Convert to units of number of times/day using the
conversion: y times/dy = x times/wk*(52 wks/365 dys)*/
        &VegLab. = &VegLab.*(52/365);
        &YogLab. = &YogLab.*(52/365);
        &FriesLab. = &FriesLab.*(52/365);
        &RiceLab. = &RiceLab.*(52/365);
        &JuiceLab. = &JuiceLab.*(52/365);
        &RedMeatLab. = &RedMeatLab.*(52/365);
        &CerealLab. = &CerealLab.*(52/365);

        run;
    %end;
%else %if &Units. = "Months" %then
%do;
        data interim1;
            set &indat.;

            /*Convert to units of number of times/day using the
conversion: y times/dy = x times/mo*(12 mos/365 dys)*/
            &VegLab. = &VegLab.*(12/365);
            &YogLab. = &YogLab.*(12/365);
            &FriesLab. = &FriesLab.*(12/365);
            &RiceLab. = &RiceLab.*(12/365);
            &JuiceLab. = &JuiceLab.*(12/365);
            &RedMeatLab. = &RedMeatLab.*(12/365);
            &CerealLab. = &CerealLab.*(12/365);

            run;
        %end;
%else
%do;
        /*Put error statement in log with %put*/
        %put %str(ERROR: INVALID INPUT FOR ARGUMENT "Units");
    %end;

/*Cap maximum daily consumption at 13 times per day*/
/*Create intermediate dataset 2.*/
data interim2;
    set interim1;

    if &VegLab. >= 13 then &VegLab. = 13;
    else &VegLab. = &VegLab.;

    if &YogLab. >= 13 then &YogLab. = 13;
    else &YogLab. = &YogLab.;

    if &FriesLab. >= 13 then &FriesLab. = 13;
    else &FriesLab. = &FriesLab.;

    if &RiceLab. >= 13 then &RiceLab. = 13;
    else &RiceLab. = &RiceLab.;

    if &JuiceLab. >= 13 then &JuiceLab. = 13;
    else &JuiceLab. = &JuiceLab.;

    if &RedMeatLab. >= 13 then &RedMeatLab. = 13;
    else &RedMeatLab. = &RedMeatLab.;

```

```

        if &CerealLab. >= 13 then &CerealLab. = 13;
        else &CerealLab. = &CerealLab.;
run;

/*Compute raw index score and scaled index score*/
data interim3;
    set interim2;

    /*RawScore*/
    if (&VegLab. = .) OR (&YogLab. = .) OR (&FriesLab. = .) OR
        (&RiceLab. = .) OR (&JuiceLab. = .) OR (&RedMeatLab. = .) OR
        (&CerealLab. = .) then RawScore = .;
    else RawScore = 33.0108 /*Beta intercept = 33.0108*/
        + (-0.4106)*&VegLab. /*Beta veg = -0.4106*/
        + (-0.5590)*&YogLab. /*Beta yog = -0.5590*/
        + (-0.8566)*(13 - &FriesLab.) /*Beta fries = -0.8566*/
        + (-0.5752)*(13 - &RiceLab.) /*Beta rice = -0.5752*/
        + (-0.1870)*(13 - &JuiceLab.) /*Beta juice = -0.1870*/
        + (-0.5793)*(13 - &RedMeatLab.) /*Beta red meat = -0.5793*/
        + (-0.4406)*(13 - &CerealLab.) /*Beta cereal = -0.4406*/
        ;

    /*Scaled Score*/
    /*First make variables of theoretical min and max raw index
scores*/
    /*Theoretical min raw score (healthiest score): eating max of
healthy and none of unhealthy items*/
    MinScore = 33.0108 /*Beta intercept = 33.0108*/
        + (-0.4106)*13 /*Beta veg = -0.4106*/
        + (-0.5590)*13 /*Beta yog = -0.5590*/
        + (-0.8566)*(13 - 0) /*Beta fries = -0.8566*/
        + (-0.5752)*(13 - 0) /*Beta rice = -0.5752*/
        + (-0.1870)*(13 - 0) /*Beta juice = -0.1870*/
        + (-0.5793)*(13 - 0) /*Beta red meat = -0.5793*/
        + (-0.4406)*(13 - 0) /*Beta cereal = -0.4406*/
        ;

    /*Theoretical max raw score (unhealthiest score): eating min of
healthy and max of unhealthy items*/
    MaxScore = 33.0108 /*Beta intercept = 33.0108*/
        + (-0.4106)*0 /*Beta veg = -0.4106*/
        + (-0.5590)*0 /*Beta yog = -0.5590*/
        + (-0.8566)*(13 - 13) /*Beta fries = -0.8566*/
        + (-0.5752)*(13 - 13) /*Beta rice = -0.5752*/
        + (-0.1870)*(13 - 13) /*Beta juice = -0.1870*/
        + (-0.5793)*(13 - 13) /*Beta red meat = -0.5793*/
        + (-0.4406)*(13 - 13) /*Beta cereal = -0.4406*/
        ;

    /*Equation for computing scaled index score*/
    if RawScore = . then IndexScore = .;
    else IndexScore = (100*(RawScore - MaxScore))/(MinScore -
MaxScore);

    label IndexScore = "Maternal diet index score";
run;

```

```

/*Create final dataset with only input dataset variables and the final
index score*/
proc sort data = &indat.;
    by &idLab.;
run;

proc sort data = interim3;
    by &idLab.;
run;

options notes;
data &outdat.;
    merge &indat.
          interim3 (keep = &idLab. IndexScore);
    by &idLab.;
run;

options nonotes;
/*Remove interim datasets from working library*/
proc datasets library = work nolist nodetails;
    delete interim1 interim2 interim3;
run;
quit;

options notes;

%mend; /*End ComputeDietIndex macro*/

```

Example input SAS dataset:

Example data: reported weekly intake frequencies for 10 participants

Obs	PID	Veg	Yog	Fries	Rice	Juice	Meat	Cereal
1	001	21	5	7	4	7	2	5
2	002	5	3	10	7	14	5	10
3	003	15	7	2	10	5	0	2
4	004	25	10	0	5	0	3	0
5	005	18	6	5	2	1	7	7
6	006	7	4	3	6	3	1	4
7	007	30	8	1	8	10	6	14
8	008	11	2	6	0	4	4	3
9	009	13	0	12	6	8	11	1
10	010	18	1	4	3	6	5	5

Description of variables in example dataset:

Alphabetic List of Variables and Attributes				
#	Variable	Type	Len	Label
8	Cereal	Num	8	Weekly reported intake of cold cereal
4	Fries	Num	8	Weekly reported intake of French fries and other fried potatoes
6	Juice	Num	8	Weekly reported intake of 100% pure fruit juice
7	Meat	Num	8	Weekly reported intake of red meats
1	PID	Char	8	Participant identification number
5	Rice	Num	8	Weekly reported intake of rice and cooked grains
2	Veg	Num	8	Weekly reported intake of vegetables
3	Yog	Num	8	Weekly reported intake of yogurt

Example SAS code for utilizing macro to compute maternal diet index scores for example input dataset

```
data inputdat;
    set in01.ExampleData;
run;

/*Run the macro for the input dataset, providing the variable names and the
appropriate units for the dataset.
Requests that the output dataset be named ExampleOut*/
%ComputeDietIndex(indat=inputdat, idLab=PID, VegLab=Veg, YogLab=Yog,
FriesLab=Fries, RiceLab=Rice, JuiceLab=Juice, RedMeatLab=Meat,
CerealLab=Cereal, Units="Weeks", outdat=ExampleOut);

/*Examine the output dataset*/
proc print data = ExampleOut;
run;

proc contents data = ExampleOut;
run;
```

Example output from running example SAS code to compute maternal diet index scores for example dataset

The SAS System										
Obs	PID	Veg	Yog	Fries	Rice	Juice	Meat	Cereal	IndexScore	
1	001	21	5	7	4	7	2	5	72.6579	
2	002	5	3	10	7	14	5	10	67.4240	
3	003	15	7	2	10	5	0	2	73.3687	
4	004	25	10	0	5	0	3	0	76.5427	
5	005	18	6	5	2	1	7	7	72.5167	
6	006	7	4	3	6	3	1	4	71.9704	
7	007	30	8	1	8	10	6	14	73.0732	
8	008	11	2	6	0	4	4	3	71.9466	
9	009	13	0	12	6	8	11	1	68.0561	
10	010	18	1	4	3	6	5	5	72.0888	

References

1. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. . <https://www.R-project.org/>. Published 2019.
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