

1 **Human Postprandial Responses to Food and Potential for Precision**
2 **Nutrition**

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33 Metabolic responses to food influence cardiometabolic disease risk, but large-scale high-resolution
34 studies are lacking. We recruited n=1,002 twins and unrelated healthy adults in the UK into the
35 PREDICT1 study and assessed postprandial metabolic responses in a clinic setting and at home. We
36 observed large inter-individual variability (population coefficient of variation [SD/mean]%) in
37 postprandial blood triglyceride (103%), glucose (68%), and insulin (59%) responses to identical
38 meals. Person-specific factors, such as the gut microbiome, had a greater influence (7.1% of
39 variance) than meal macronutrients (3.6%) for postprandial lipemia, but not for postprandial
40 glycemia (6.0% and 15.4% respectively); genetic variants had a modest impact on predictions (9.5%
41 for glucose, 0.8% for triglyceride, 0.2% for c-peptide). Findings were independently validated in a US
42 cohort (n=100). We developed a machine learning model that predicted both triglyceride (r=0.47)
43 and glycemic (r=0.77) responses to food intake. These findings may be informative for developing
44 personalized diet strategies. ClinicalTrials.gov registration: NCT03479866.

45

46 **Introduction**

47 Effective prevention strategies are required to reduce the immense global burden of nutrition-
48 related non-communicable diseases (NCD)¹. Nutritional research and the corresponding guidelines²⁻⁴
49 focus on population averages. However, the high between-person variability in response to foods
50 and weight-loss diets⁵ demands development of more personalized approaches. Empirically-based
51 precision nutrition requires research using multi-dimensional, high-resolution time-series data from
52 adequately powered studies⁶. The application of technologies to accurately and precisely quantify
53 many postprandial (non-fasting) traits in large cohorts and in real-world settings is extending
54 capabilities in this field of research.

55

56 Although fasting blood assays are used in many clinical diagnoses, most people are predominantly in
57 the postprandial state during waking hours. Postprandial lipid, glucose and insulin dyshomeostasis

58 are independent risk factors for NCDs and obesity^{7,8,9}. Postprandial hyperglycemia raises risk of
59 cardiovascular disease (CVD), coronary heart disease (CHD)¹⁰ and cardiovascular mortality, even in
60 individuals with normal fasting glucose¹¹, and postprandial triglyceride is more predictive of CVD
61 than fasting concentrations^{12,13}, highlighting the relevance of diet and its metabolic consequences in
62 cardiovascular risk.

63

64 A person's unique postprandial glycaemic and lipidaemic responses are likely attributable their
65 biological (e.g. microbiome and nuclear DNA variation) and lifestyle characteristics^{2,14}, as
66 demonstrated previously for specific meals⁵. While postprandial glycaemic responses are important
67 health determinants, glycaemic control is just one part of a more complex metabolic equation
68 involving triglyceride (the primary alternative energy substrate to glucose) and insulin (regulating
69 glucose and triglyceride transport and metabolism)¹⁵. Thus, also characterizing postprandial
70 regulation of lipids and identifying the factors responsible for individual variations could help
71 optimize diet recommendations targeting broader improvements in cardiometabolic health.

72

73 The PREDICT 1 clinical trial (NCT03479866) was designed to quantify and predict individual variations
74 in postprandial triglyceride, glucose and insulin responses to standardized meals. PREDICT 1 enrolled
75 twins and unrelated adults from the UK in whom genetic, metabolic, microbiome composition, meal
76 composition and meal context data were obtained to distinguish predictors of individual responses
77 to meals. These predictions were validated in an independent cohort of adults from the USA.

78

79 Our findings show wide variations in postprandial responses between people, even identical twins,
80 attributable in large part to modifiable factors. We found that people who experience poor
81 metabolic responses to a given meal are likely to respond poorly to other meals of the same
82 macronutrient profile, and the overall correlation between postprandial glucose and triglyceride

83 responses is weak. The postprandial prediction models we have developed could help to optimize
84 personalized diet recommendations.

85

86 **Results:**

87

88 1002 healthy adults from the UK completed baseline clinic measurements consisting of postprandial
89 metabolic responses (0-6h; blood triglyceride, glucose and insulin concentrations) to sequential
90 mixed-nutrient dietary challenges. Findings were validated a US cohort of 100 healthy adults.

91 Additional data was collected over the subsequent 13-day period at home, where postprandial
92 responses to eight meals (seven in duplicate) of different macronutrient (fat, carbohydrate, protein
93 and fiber) content were measured using continuous glucose monitors (CGM) and dried blood spot
94 (DBS) analysis. The study design is described in detail in the Methods and Figure 1, the inclusion

95 criteria and descriptive characteristics of study subjects are presented in **Supplemental Table 1**.

96 Further information on the research design is available in the Life Sciences Reporting Summary
97 linked to this article.

98

99 ***Inter- and intra-individual variation in postprandial responses***

100 Inter-individual variability in postprandial responses was examined in a tightly controlled clinic
101 setting following the sequential standardized test meal challenge after fasting (**Figure 2a**). The inter-
102 individual patterns of response for each outcome was assessed using Levene's test of variance.
103 Heterogeneity across all postprandial time-points (fasting to 6-hrs) varied greatly for triglyceride
104 ($p=3.931e-11$), glucose ($p=2.91e-194$) and insulin ($p=2.45e-17$) concentrations. In serum, the
105 population coefficient of variation was higher for postprandial triglyceride_{6hr-rise} (103%) and
106 glucose_{iAUC0-2h} (68%) compared with fasting values (50% and 10%, respectively). This was not true for
107 insulin_{iAUC0-2h} (59%) compared to fasting (69%; **Figure 2a**), suggesting that these measures of

108 postprandial triglyceride and glucose concentrations, but not insulin, provide better discrimination
109 of an individual's metabolic tolerance than fasting values.

110

111 A key assumption when developing personalized prediction algorithms is that an individual's unique
112 response to the same meal is reproducible. Much of the between-person phenotypic variability
113 observed in studies examining response to diet interventions that include only a single test-
114 response scenario could be a result of regression to the mean and other sources of error. Repeated-
115 measures (multiple measures taken within individual at a single time-point and across multiple time
116 points) can be used to partition error from true biological variability, thereby improving the precision
117 of the estimate. Accordingly, we administered test meals of varying macronutrient composition in
118 duplicate per participant, under similar conditions (see Methods and **Supplemental Table 2** for
119 details). We also used continual glucose monitors (CGMs), which provided sequential measures of
120 blood glucose at 5 minute intervals during the study period. Intra-individual variability (repeatability)
121 was assessed using intra-class correlation coefficients (ICC) for triglyceride, C-peptide (from DBS
122 assays) and glucose (from CGM) measurements. The ICCs were: triglyceride_{6hr-rise}=0.46 [95% CI 0.37,
123 0.54]; glucose_{AUC0-2h}=0.74 [95% CI 0.72, 0.75]; C-peptide_{2hr-rise}=0.62 [95% CI 0.54, 0.69] (**Supplemental**
124 **Table 3**). The differences in ICCs between triglyceride, C-peptide and glucose measurements partly
125 reflect the different assays used (DBS and CGM) (see Methods).

126

127 ***Predicting individual postprandial responses within a population***

128 We assessed the overall extent to which input variables (**Supplemental Table 3**) predict personal
129 postprandial responses (**Figure 2b-d**), initially using multivariable linear regression. Input variables
130 include: i) baseline characteristics (age, sex, clinical biochemistry (lipid, glycaemic and other
131 measures), anthropometry)); ii) genetics (single nucleotide polymorphisms (SNPs)); iii) gut
132 microbiome features); iv) habitual diet (from Food Frequency Questionnaire (FFQ)); v) meal context
133 (sleep, previous meals, physical activity, meal sequence and /or timing); vi) meal composition

134 (energy from carbohydrate, sugar, fat, protein and fiber). Postprandial glyceemic responses were
135 determined from serum and CGM measurements in the clinic and at home (from 7 standardized
136 meals and 6,616 readings; see Methods). Postprandial C-peptide and triglyceride were determined
137 (from two standardized meals) from serum and DBS assays collected during the clinic and home
138 phases . We also tested the correlation between fasting and postprandial characteristics and found
139 that the correlation between postprandial triglyceride, with regards to postprandial glucose and
140 postprandial C-peptide measures was low (**Figure 3a**).

141 **Individual baseline characteristics.** The proportions of trait variance explained by individual baseline
142 characteristics are shown in **Figures 2b, c and d** for triglyceride_{6h-rise}, glucose_{iAUC0-2h}, and C-peptide_{1h-}
143 _{rise} respectively (**Supplemental Table 3**).

144 **Genetic factors** . The heritability of postprandial responses in the UK cohort was examined using
145 classical twin methods (variance components analyses) to establish the upper bound of what might
146 be predicted by directly measured genetic variation. Two-thirds of the cohort was recruited from the
147 TwinsUK registry ¹⁶, of which 230 twin pairs (n=460; 183 MZ and 47 DZ) were studied for heritability.
148 Additive genetic factors explained 30% of the variance in glucose_{iAUC0-2h}, whereas only 4% of the
149 variance in triglyceride_{6h-rise} and 9% of the variance in insulin_{2h-rise} were explained in this way
150 (**Figure 3b**). The estimated genetic variances in insulin_{1h-rise} and C-peptide_{1h-rise} were close to zero
151 (**Supplemental Table 4**).

152 **SNP-based genetic factors.** In a subgroup of participants who are part of the TwinsUK cohort and
153 had genome wide genotyping previously measured with available GWAS data (n=241), we tested
154 whether 32 SNPs derived from previous genome-wide scans of postprandial glucose, insulin or
155 triglyceride concentrations ¹⁷⁻²¹ were also associated with the postprandial variables studied here.
156 Several SNPs were significantly (p<0.05) associated with these variables (**Figure 3c** and
157 **Supplemental Table 4**), but collectively explained only ~9% of observed variation in glucose_{iAUC0-2h}

158 (Figure 2c), and less than 1% of variation for postprandial triglyceride and postprandial C-peptide
159 (Figure 2b and 2d).

160 **Gut microbiome (16S rRNA).** We estimated the contribution of gut microbiome composition using
161 relative bacterial taxonomic abundances and measures of community diversity and richness, derived
162 from 16S rRNA high-throughput sequencing of baseline stool specimens (Supplemental Table 4). We
163 found that without adjusting for any other individual characteristics the gut microbiome
164 composition explained 7.5% of postprandial triglyceride_{6h-rise}, 6.4% of postprandial glucose_{iAUC0-2h} and
165 5.8% of postprandial C-peptide_{1h-rise}.

166 **Meal composition, habitual diet and meal context.** To determine the impact of the macronutrient
167 composition of meals, we measured triglyceride_{6h-rise} and C-peptide_{1h-rise} for two standardized home
168 phase meals of contrasting macronutrient compositions (for triglyceride, comparison of meals 1 and
169 7: 85 vs 28g of carbohydrate and 50 vs 40 g of fat at breakfast, both followed by a lunch of 71g
170 carbohydrate and 22g fat; for C-peptide, comparison of meal 2 and 3: 71 vs 41 g of carbohydrate and
171 22 vs 35 g of fat; Supplement Table 2) in subsets of participants (n=712 and n=186,
172 respectively). Glucose_{iAUC0-2h} was measured for seven standardized meals (comparison of meals 1, 2,
173 4, 5, 6, 7 and 8: 28 - 95 g carbohydrate; 0 - 53 g fat) totalling 9,102 meals in 920 individuals. The
174 proportions of variance explained by meal composition, habitual diet, and by meal context are
175 shown for triglyceride_{6h-rise} in Figure 2b, for glucose_{iAUC0-2h} in Figure 2c, and for C-peptide_{1h-rise} in Figure
176 2d. A multivariate regression model (meals 1, 2, 4, 5, 6, 7 and 8) revealed that the Glucose_{iAUC0-2h}
177 (mmol/L*s) was significantly (P<0.001) reduced by 79, 142 and 185 for every 1g fat, fiber and protein
178 respectively, after adjustment for carbohydrate consumption.

179

180 **Machine learning model.** To estimate the unbiased predictive utility of the factors analysed, we
181 used a machine learning approach robust to overfitting²². Random Forest regression models²³ were
182 fitted using all the informative features (meal composition, habitual diet, meal context,
183 anthropometry, genetics, microbiome, clinical and biochemical parameters) to predict triglyceride_{6h-}

184 $_{rise}$, $glucose_{iAUC0-2h}$ and $C-peptide_{1h-rise}$ in the UK cohort dataset. The predicted values were compared
185 with the observed values for each trait using Pearson correlation coefficients (r); these correlations
186 were $r=0.47$, $r=0.77$ and $r=0.30$ for $triglyceride_{6h-rise}$, $glucose_{iAUC0-2h}$ and $C-peptide_{1h-rise}$, respectively.
187 Similar correlations were observed in the held-out validation set (US cohort) and the model predictions
188 for $triglyceride_{6h-rise}$ and $glucose_{iAUC0-2h}$ were $r=0.42$ and $r=0.75$, respectively, but much weaker for C-
189 $peptide_{1h-rise}$ ($r=0.14$) (**Figure 4**). The features used to fit the models are reported in **Supplemental**
190 **Table 5**. The repeatability and robustness of the machine-learning model is presented in the
191 **Extended Data Figure 4**.

192 ***Postprandial responses in relation to surrogate scores of clinical outcomes.*** We compared the
193 extent to which fasting and postprandial concentrations for the different biomarkers could be used
194 to predict impaired glucose tolerance (7.8-11.0 mmol/L 2 hours after an OGTT) and atherosclerotic
195 cardiovascular disease (ASCVD) 10-yr risk score (Methods) by comparing the area under the receiver
196 operator characteristics (ROC-AUC) curves; **Figure 5**. We found that fasting triglyceride and
197 $triglyceride_{6h-rise}$ contributed similarly to the ROC-AUC for ASCVD risk, and that including both was
198 more informative than including only one of them (Figure 5a). We also found that, although
199 postprandial glucose was not as informative as fasting glucose, adding $glucose_{iAUC0-2h}$ to fasting
200 glucose resulted in a slightly higher ROC-AUCs (0.72 vs 0.69) for ASCVD 10-yr risk. Fasting C-peptide
201 and fasting glucose were as effective (ROC AUC= 0.69) as fasting triglyceride in ASCVD prediction,
202 whereas postprandial C-peptide (ROC AUC= =0.63) and postprandial glucose were weaker (ROC
203 AUC= 0.62) than postprandial triglyceride (ROC AUC= 0.71). Fasting and postprandial triglyceride
204 concentrations were weakly predictive (ROC AUC= 0.55 and 0.59, respectively) of impaired glucose
205 tolerance (IGT), whereas fasting and postprandial C-peptide were moderately predictive (ROCAUC=
206 0.64 and 0.65 respectively), although with no added predictive value in combination. We did not
207 include here the prediction of IGT using CGM glucose. This is because IGT is defined solely based on
208 the blood glucose concentration at 2hrs during an OGTT, which is captured by the CGM glucose

209 recording, and so the derivation of the predictor and the clinical score variables would be heavily
210 dependent upon one another. Results were similar in the UK and US cohorts (Figure 5).

211

212 ***Decoding individual responses***

213 Having investigated postprandial responses within the population, we then explored the responses
214 at the individual level. We examined glycemic responses, as the granular CGM data collected during
215 the at-home phase enabled us to assess real-world effects in detail, which was not possible for
216 triglyceride or C-peptide. We investigated how much of an individual's postprandial response is a
217 attributable to a meal's glycemic properties, compared with how the variation resulting from other
218 modifiable factors such as meal timing, exercise and sleep.

219 We first examined the contribution of the meal. Although it is a widely held notion that, for an
220 individual, variations in meal composition are primarily responsible for the variation in responses to
221 food and that ranking of meal responses should be the same for all people^{24,25}, we explored whether
222 meal-specific responses unique to the individual exists. We ranked the order of each participant's
223 $\text{glucose}_{\text{iAUC0-2h}}$ for every possible pair of standardized meals consumed at home. We then determined
224 how frequently these rankings differed for each participant. For most pairs of meals, the ranking was
225 the same for all individuals (e.g. OGTT has a higher $\text{glucose}_{\text{iAUC0-2h}}$ than high-fiber muffins in all
226 participants, **Figure 6a**). However, for select pairs of meals, the ranking was reversed in up to 48% of
227 participants, such as between the medium fat and carbohydrate at lunch vs high carbohydrate
228 breakfast (350 of 727 participants) (meal 2 vs. meal 4; **Supplemental Table 2**). In 186 out of 498
229 (37.3%) participants, discrepancies were also seen between the high fat and the high protein meals
230 (meals 7 and 8). The distribution of how these meals were ranked for the participants of the
231 PREDICT study is presented in **Extended Data 2**.

232 We note that the reordering of meal rankings could have been the result of noise. We therefore
233 used ANOVA to estimate the effect size for the different factors explaining glycemic response (**Figure**
234 **6b**), including person-specific effects (effects that vary between people but not between meals). As

235 described in the **Methods**, we considered not only the effect of the meal macronutrient and energy
236 content in the response (meal composition), but also considered how each individual responded on
237 average to all their set meals relative to the population (individual glucose scaling), as well as the
238 effect of the individual's meal-specific response, the error attributable to the glucose measurement
239 and other sources of variation (including modifiable sources of variation such as sleep, circadian
240 rhythm and exercise).

241 We found that, consistent with the linear models described earlier, the ANOVA models show that
242 there are three meal-related factors explaining individual glycemic responses. Meal macronutrient
243 composition alters iAUC by 16.73% (95%CI 15.37 - 18.92%), but the individual glucose scaling is
244 larger, altering iAUC by roughly 18.74% (17.96% - 19.46%), while the individual's meal-specific
245 response is much smaller, affecting the final meal iAUC by 7.63% (6.11% - 8.96%). Other modifiable
246 sources of variation not directly related to the meal composition, such as meal timing, exercise and
247 sleep, contributed similar amounts of variance as the meal's composition (**Figures 6b and c**).

248 To investigate whether modifying the order in which meals are consumed and time of the day affect
249 glycemic responses, we looked at participants eating an identical meal (meal 2) for breakfast and
250 lunch. The average glycemic response for the same individuals was on average 2-fold higher (t-
251 statistic = -35.7, 2721 d.f.; P< 0.001) when the meal was ingested for lunch (mean glucose 2h
252 iAUC=14254 SD=6593) (4h following the metabolic challenge breakfast) than when ingested for
253 breakfast (mean glucose 2h iAUC=7216, SD=4157), although with wide individual variation (**Figure**
254 **6c**).

255 **Discussion:**

256 Nutrition and health are intimately linked. Each day people make diet-related decisions that are
257 influenced by perceived enjoyment and satiation, as well as health benefits and harm attributed to
258 specific foods and beverages. Standard nutritional guidelines²⁻⁴ are typically based on population
259 averages. However, it is increasingly evident that one-size nutritional recommendations do not fit
260 all, which is exemplified by the variable efficacy of tightly controlled lifestyle intervention trials²⁶⁻²⁹.

261 To address these challenges, we undertook a two-week interventional trial, including a tightly-
262 controlled in-clinic day and a two-week at-home phase, where postprandial metabolic responses to
263 a series of standardized meals were obtained in more than 1,000 healthy adults from the UK and
264 USA. The primary aim was to derive algorithms that predict an individual's postprandial metabolic
265 responses to specific foods. The core outcomes were variations in blood concentrations of
266 triglyceride, glucose and insulin (or C-peptide), as these biomarkers work in concert to affect
267 cardiometabolic risk^{8,30}.

268 In many cases, we observed responses that contrast with those reported in traditional clinic-based
269 studies, thereby reshaping conclusions about the key factors influencing responses to foods. For
270 example, genetic influence was less than expected, especially for triglyceride, while modifiable
271 factors like meal timing conveyed larger effects than anticipated.

272 Meal composition has large effects on postprandial insulinemic and lipidemic response³¹ Some small
273 studies suggest that meals with high-fat and/or protein content elicit very different postprandial
274 responses than lower-fat and/or protein meals with identical carbohydrate content (reviewed in ³¹).
275 The type of fat in a meal also alters the lipemic response³². However, measuring postprandial
276 triglyceride and C-peptide at-home in large cohorts is both logistically challenging and places a
277 considerable burden on. Thus, for pragmatic reasons, only two pairs of meals (high fat and high
278 carbohydrate, respectively) were used to calculate postprandial triglyceride and C-peptide responses
279 and the difference in macronutrient content of these meals was low. This **limited number of**
280 **different meals and their relatively similar macronutrient content** might explain why the effects
281 seen for postprandial triglyceride and C-peptide were lower than expected.

282 In addition to fasting concentrations of triglyceride and glucose, we found that postprandial
283 triglyceride and glucose concentrations were informative for IGT and CVD risk determination.
284 However, postprandial C-peptide measurements provided no additional information over fasting

285 concentrations. We found that although postprandial triglyceride and glucose responses were highly
286 variable between individuals, a person's response to the same meals was often similar and therefore
287 predictable. Any given individual generally responds comparably to different meals of the same
288 macronutrient profile, with some people experiencing large postprandial excursions across most
289 meals, whereas others consistently experience modest responses. This is important for
290 individualized prediction and recommendations, as it suggests that once one has learned about an
291 individual's postprandial response to specific foods, their response to other foods could be inferred.

292 We show that a person's glycemic response is the result not only of individual-specific glucose
293 scaling, which determines whether a person is a high or low responder to all meals, but that there
294 are also meal-specific responses unique to an individual. Possible explanations include individual
295 genetic differences in the ability to digest high-starch meals³³. Zeevi and co-workers⁵ reported an
296 example where one participant had an exaggerated glycemic response to a banana but not to a
297 cookie, whereas the second participant had the opposite response. We assessed this phenomenon
298 in our data and found that individual glucose scaling and meal-specific responses both exist, but
299 individual meal-specific responses are generally much more effective than scaling.

300 People differ greatly in their responses to diet interventions. The DIETFITS study, for example,
301 randomised 609 people to either a healthy low fat or a healthy low carbohydrate diet for 12-
302 months³⁴. By study end, average weight loss was similar between groups (~5-6kg), but wide
303 variations were seen within groups (-30kg to +10kg). Elsewhere, the Diabetes Prevention Program
304 showed that although a standardized intensive lifestyle intervention focusing on changes in diet
305 (tailored only to the energy requirements of the individual) lowered diabetes risk substantially²⁸, its
306 efficacy varied greatly across the study population^{26,27}, and was determined to some extent by
307 genetic factors²⁹. While response to diet interventions will depend partly on adherence, findings
308 from the PREDICT trial and elsewhere^{35,36} suggest that even in highly-adherent participants,

309 substantial response variations exist, which might be predictable. In PREDICT, non-food-specific
310 factors (e.g., meal timing, sleep, activity) were highly informative of these person-specific responses.

311 Previous large-scale studies of postprandial responses have focused solely on glycemic outcomes
312 because assessing postprandial triglyceride and insulin concentrations in free-living conditions is
313 challenging ²²⁵. Here, we assessed glycemic responses with CGMs, but also assessed triglyceride and
314 C-peptide concentrations during the at-home period of the study using a validated DBS method and
315 support from a specifically designed mobile app (**Methods**). The low correlation between triglyceride
316 and glucose suggests that prediction algorithms relying solely on glucose would be insufficient for
317 the detection of dysregulated triglyceride responses.

318 The prediction algorithms we developed are likely to have been strengthened by the use of
319 randomized, mixed meals, containing combinations of macronutrients reflective of those seen in
320 real-world settings, rather than supra-physiological lipid or carbohydrate challenges, as used in
321 previous studies.

322 In general, genetics, contrary to our expectations, was not a predominant determinant of these
323 responses; we found that the heritable fraction (the trait variance explained by additive genetic
324 factors) of C-peptide and/or insulin concentrations at 1 hr was very low (0.3%) and at 2 hrs remained
325 low (9.1%). The heritable fractions for postprandial triglyceride (6hr rise) and glucose (2hr iAUC)
326 responses were higher, but still modest (16% and 30%, respectively). Despite the wealth of publicly
327 available SNP data (see: www.type2diabetesgenetics.org), there is no robust data for these specific
328 postprandial traits, as almost all published GWAS of serological traits have focused on fasting values.
329 Nevertheless, in exploratory analyses, we examined the predictive value of loci previously linked to
330 post-challenge triglyceride, glucose or insulin concentrations ¹⁷⁻²¹ but found that the predictive utility
331 of these variants was poor, particularly for triglyceride and C-peptide (**Figure 3c**). The modest
332 heritability of postprandial traits means that even in an unrealistically optimistic scenario, where

333 most of this trait variance is explained by known DNA variants, it is unlikely that prediction
334 algorithms using DNA variant data alone, which many direct-to-consumer nutrigenomics companies
335 advocate, would succeed.

336 The lack of a major genetic component to these traits highlights the likely involvement of modifiable
337 environment exposures. Indeed, we found that meal composition and context (e.g. meal timing,
338 exercise, sleep and circadian rhythm) were core determinants of postprandial metabolism. These
339 predictions were strengthened using data on gut microbiome diversity. Using machine learning
340 combining all relevant data, an individual's postprandial triglyceride and glycemic responses could
341 be meaningfully predicted, with similar results in the US validation cohort. For C-peptide, the
342 prediction was much weaker in the validation cohort ($r=0.30$ UK, $r=0.14$ US), possibly reflecting the
343 lower number of test meals relative to the number of input variables, which could adversely affect
344 the reliability of the prediction³⁷. The postprandial glycemic predictions were similar to those
345 reported by Zeevi and colleagues⁵, although the analysis methods and input features are not directly
346 comparable.

347 Despite having developed these prediction algorithms, there is scope for improvement, such as
348 inclusion of a more diverse array of meal interventions and with more detailed assessments of
349 contextual factors than in the current study. Technological advances could also help to improve
350 predictions. For example, although glucose can be continuously assessed with CGMs, no
351 commercially available devices suitable for free-living assessments of continuous insulin and
352 triglyceride concentrations currently exist. Moreover, owing to the differences in tolerability and the
353 lower limit of detectable responses of dietary carbohydrates compared with fats³⁸, our trial suggests
354 that the prediction of postprandial glucose is methodologically superior to triglyceride responses
355 (see Fig 2b-d). Difficulties in directly comparing changes in triglyceride and glucose were a limitation
356 of our study. Continuous, accurate measures of these traits could substantially improve predictions
357 owing to reductions in model error and the ability to study non-linear patterns of response, which

358 may be important. The inclusion of deep ‘-omics’ data may further enhance the predictive ability of
359 these algorithms; for example, here we used microbiome data derived from 16S RNA sequencing,
360 which, whilst proving valuable for prediction (explaining 6.4% and 7.5% of the variances for glucose
361 and triglyceride responses, respectively), may prove even more informative if derived from higher-
362 resolution metagenomic sequencing. The nutritional signatures detectable within the metabolome,
363 both in blood³⁹ and feces⁴⁰, suggest that including a larger metabolomics panel and quite probably
364 other -omics data, e.g. meta-transcriptomics, transcriptomics or proteomics, in our algorithms would
365 add costs but also enhance predictions. Using FFQs, we found that habitual diet explains a small
366 proportion (<2%) of an individual’s postprandial responses. However, FFQs have well-known
367 limitations, and other objective approaches may be considerably less biased and error prone²⁷.
368 Pairing this with short-term assessments, like the weighed dietary record included in the PREDICT
369 study app, may help mitigate these limitations. More comprehensive challenge tests might also
370 reveal new aspects of postprandial metabolism; here, we used a 6-hr meal tolerance test, as this was
371 deemed the maximum duration that most participants were likely to accept. Data from longer
372 duration challenge tests (up to 8hrs), for both glucose and triglyceride responses, may provide
373 valuable information.

374 For postprandial triglyceride and glucose responses, the prediction models derived in the UK cohort
375 performed almost as well in the independent US validation cohort, which is reassuring given
376 differences in environmental factors; nevertheless, both cohorts were comprised of younger healthy
377 adults of European ancestry. Thus, the generalization of our findings would require validation in
378 people of non-European ancestry, older adults, and in people with diseases that affect metabolism
379 such as diabetes. The clinical implications of our predictions will require appropriately powered
380 longitudinal studies.

381 In conclusion, this is the most comprehensive assessment to date of metabolic responses to
382 nutritional challenges in a rigorous intervention setting. We observed considerable inter-individual

383 differences in postprandial metabolic responses to the same meals, challenging the logic of
384 standardized diet recommendations. These findings, in addition to the scalability of the assessment
385 methods and the accuracy of the prediction algorithms described here, mean that, at least from a
386 cardiometabolic health perspective, population-wide personalized nutrition has potential as a
387 strategy for disease prevention.

388

389 **Author contributions**

390 Obtained funding: J.W., G.H., T.D.S.. Study design and developed concept: S.E.B., A.M.V., J.W., G.H.,
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413

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415 Delahanty, N Segata, are consultants to Zoe Global Ltd ("Zoe"). J Wolf, G Hadjigeorgiou, R Davies, H
416 Al Khatib, J Capdevila, C Bonnett, S Ganesh, E Bakker, P Wyatt and I Linenberg are or have been
417 employees of Zoe. Other authors have no conflict of interest to declare.

418

419 **Data availability**

420 The data used for analyzing this study are held by the department of Twin Research at Kings College
421 London. The data can be released to bona fide researchers using our normal procedures overseen by
422 the Wellcome Trust and its guidelines as part of our core funding. We receive around 100 requests
423 per year for our datasets and have a meeting three times a month with independent members to
424 assess proposals. Application is via [https://twinsuk.ac.uk/resources-for-researchers/access-our-](https://twinsuk.ac.uk/resources-for-researchers/access-our-data/)
425 [data/](https://twinsuk.ac.uk/resources-for-researchers/access-our-data/). This means that the data needs to be anonymized and conform to GDPR standards.
426 Specifically for this paper, all the variables used in the models can be requested as well as the
427 summary outcome measures for each person. The 16S microbiome data used here will be uploaded
428 onto the EBI website (<https://www.ebi.ac.uk/> with unlimited access.

429

430 **Code availability**

431 The scripts for statistical analysis are freely available upon request to the Department of Twins
432 Research. Application is via <https://twinsuk.ac.uk/resources-for-researchers/access-our-data/>.

433

434 **Figure Legends**

435

436 **Figure 1. Experimental design.** The PREDICT 1 study comprised a primary UK-based cohort

437 ($n_{max}=1,002$) and an independent US-based validation cohort ($n_{max}=100$).

438

439 **Figure 2. Variation in postprandial responses. a.** Inter-individual variation in triglyceride, glucose
440 and insulin postprandial responses to the breakfast and lunch meal challenges in the clinic ($n=1002$).

441 **b.** Determinants of triglyceride_{6h-rise} measured from DBS (comparison of meals 1 and 7). **c.**

442 Determinants of glucose_{iAUC0-2h} measured by CGM (comparison of 7 test meals; 1, 2, 4, 5, 6, 7 and 8).

443 **d.** Determinants of C-peptide_{1h-rise} measured from DBS as a proxy for insulin (comparison of meals 2

444 and 3). Trait variations explained for each input variable are derived from separate (non-hierarchical)
445 regression models. Values represent adjusted-R² and error bars reflect 95% confidence intervals.

446 Meal composition and Meal context adjusted-R² values were derived from meal sample sizes as

447 follows; triglyceride_{6h-rise}, $n=712$; glucose_{iAUC0-2h}, $n=9102$; C-peptide_{1h-rise}, $n=186$. All other determinant

448 values were derived from meal sample sizes as follows; triglyceride_{6h-rise}, $n=920$; glucose_{iAUC0-2h},

449 $n=958$; C-peptide_{1h-rise}, $n=960$. TG= triglyceride, DBS= dried blood spots, CGM= continuous glucose

450 monitor. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ using multivariable linear regression.

451

452 **Figure 3. Relationship of baseline values, genetic and microbiome factors to postprandial**

453 **responses. a.** Pearson correlations between baseline values and postprandial prediction measures of

454 980 participants from the UK cohort. **b.** Heritability of postprandial responses (the ACE model was

455 fitted on log-scaled postprandial responses for triglyceride, glucose, insulin and C-peptide) in 183 MZ

456 and 47 DZ twin pairs. A; additive genetic component, C; shared environmental component, E;

457 individual environmental component. **c.** SNP associations with postprandial measures focusing on

458 SNPs identified in published postprandial trait GWAS¹⁷⁻²¹ ($n=241$; * $p<0.05$, *** $p<0.001$, using two-

459 sided chi-squared test).

460

461 **Figure 4 - Machine learning models fitted in to postprandial measures. a.** Machine learning model

462 for TG_{6h-rise} in the UK cohort. **b.** Machine learning model for glucose_{iAUC0-2h} in the UK cohort. **c.**

463 Machine learning model for C-peptide_{1h-rise} postprandial responses in the UK cohort. The machine

464 learning models in the US validation cohort are shown in Figures 4 d-f. The relationship between
465 variables is expressed as Pearson's correlation coefficient (r) and denoted with a regression line; n
466 represents participant number; the features used to predict each value are the same as those listed in
467 the linear models in **Figure 2b-d**.

468 **Figure 5. Associations between fasting and postprandial values for TG, C-peptide and glucose**
469 **concentrations with clinical measures in the UK cohort.** Receiver operator characteristics curves
470 illustrating the predictive utility of fasting and postprandial TG, glucose and C-peptide measures to
471 discriminate the bottom 70% from the top 30% of the cohort (cut-off ASCVD 10 year risk of 0.0183)
472 for **a.** atherosclerotic cardiovascular disease (ASCVD) 10-year risk $n=951$ independent samples from
473 the UK and **b.** impaired glucose tolerance (IGT) $n= 826$ independent samples from the UK. The same
474 analyses were performed in the US cohort ($n=92$ independent samples) resulting in ROC AUC (95%CI)
475 values for ASCVD 10 year risk of: **C-peptide** fasting AUC=0.68 (0.56-0.80), postprandial AUC=0.66
476 (0.54-0.77), both AUC=0.69 (0.58-0.81); **TG** fasting AUC=0.73(0.63-0.84), postprandial AUC=0.75
477 (0.65-0.85), both AUC = 0.77 (0.67-0.88); and **glucose** fasting AUC= 0.74-(0.63-0.85), postprandial
478 AUC = 0.64 (0.52-0.76), both AUC = 0.76 (0.64-0.85). For impaired glucose tolerance values were: **C-**
479 **peptide** fasting AUC = 0.66 (0.53-0.80), postprandial AUC = 0.59 (0.46-0.72), both AUC = 0.67 (0.54-
480 0.80); and **Triglyceride** fasting AUC = 0.66 (0.53-0.80), postprandial AUC = 0.59 (0.46-0.72), both
481 AUC = 0.61 (0.54-0.80).

482 **Figure 6. Person-specific diversity in postprandial response. a.** Proportion of times in the PREDICT 1
483 study that the ranking of the glycemic response ($glucose_{iAUC0-2h}$) to pairs of set meals was altered
484 ($n=828$, UK cohort). **b.** Effect size for factors explaining glycemic response. The different sources of
485 variation were estimated using ANOVA, as described in Supplemental Table 3. The x-axis can be
486 approximately interpreted as percent increase (or decrease) in $iAUC$ attributable to the model
487 parameters ($n=483$ individuals) **c.** Time of day effects. ($n=920$, UK cohort). Boxes show quartiles (25th,
488 50th, 75th percentiles); whiskers show the 95% interval.

489

490

491

492

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- 589

590

591

Methods

592 **Study population, study design, recruitment criteria, meal challenges and Zoe app.**

593 **Study population**

594 The PREDICT 1 study (Personalised Responses to Dietary Composition Trial) was a multinational
595 study conducted between 5th June 2018 and 8th May 2019. The primary cohort was recruited at St.
596 Thomas' Hospital in London, UK and a validation cohort (that underwent the same profiling as in the
597 UK) assessed at Massachusetts General Hospital (MGH) in Boston, Massachusetts as described in the
598 detail in the protocol ⁴¹. In the UK, participants (target enrolment = 1,000) were recruited from the
599 TwinsUK cohort, an ongoing research cohort described elsewhere¹⁶ and online advertising (**Extended**
600 **Data Figure 1a**). In the US, participants (target enrolment = 100) were recruited through online
601 advertising, research participant databases and Rally for Research (<https://rally.partners.org/>), an
602 online recruiting portal for research trials (**Extended Data Figure 1b**). Ethical approval for the study
603 was obtained in the UK from the Research Ethics Committee and Integrated Research Application
604 System (IRAS 236407) and in the US from the Institutional Review Board (Partners Healthcare IRB
605 2018P002078). The trial was registered on ClinicalTrials.gov (registration number: NCT03479866), as
606 part of the registration for the PREDICT Programme of research, which also includes 2 other study
607 protocol cohorts. The trial was run in accordance with the Declaration of Helsinki and Good Clinical
608 Practice.

609 Study participants were healthy individuals aged between 18-65 years and able to provide written
610 informed consent. Criteria used to assess eligibility are listed in **Extended Data Table 1**. Exclusion
611 criteria included; ongoing inflammatory disease; cancer in the last three years (excluding skin
612 cancer); long term gastrointestinal disorders including IBD or Coeliac disease (gluten allergy), but not
613 including IBS; taking the following daily medications: immunosuppressants, antibiotics within the
614 last three months; capillary glucose level of >12mmol/L (or 216 mg/dL), or Type I diabetes mellitus,

615 or taking medications for type II diabetes mellitus; currently suffering from acute clinically diagnosed
616 depression; heart attack (myocardial infarction) or stroke in the last 6 months; pregnant; vegan,
617 suffering from an eating disorder or unwilling to take foods that are part of the study.

618 **Study design**

619 1,002 generally healthy adults from the United Kingdom (UK) (non-twins, and identical
620 [monozygotic; MZ] and non-identical [dizygotic; DZ] twins) and 100 healthy adults from the United
621 States (US) (non-twins; validation cohort) were enrolled and completed baseline clinic
622 measurements. Key outcomes include postprandial metabolic responses (0-6h; blood triglyceride,
623 glucose and insulin concentrations) to sequential mixed-nutrient dietary challenges (containing 86g
624 carbohydrate and 53g fat at 0h; 71g carbohydrate and 22g fat at 4h) administered in a tightly
625 controlled clinic setting on day 1 (**Figure 1**). A second set of outcomes were assessed over the
626 subsequent 13-days at home. Lipemic and C-peptide responses (as a surrogate for insulin) to two
627 standard meals differing in fat and carbohydrate composition were assessed at home using dried
628 blood spot (DBS) assays collected at three postprandial time-points. Glycemic responses to eight
629 meals (seven in duplicate) of different macronutrient (fat, carbohydrate, protein and fiber) content
630 were assessed using continuous glucose monitors (CGM). In addition, participants wore physical
631 activity and sleep monitors for the duration of the study and provided stool samples for microbiome
632 profiling.

633 We selected specific timepoints and increments for triglyceride, glucose, insulin and C-peptide to
634 reflect the different pathophysiological processes for each measure. To monitor compliance, all test
635 meals consumed by participants were logged in the Zoe app (with an accompanying picture) and
636 reviewed in real time by the study nutritionists. Only test meals that were consumed according to
637 the standardized meal protocol were included in the analysis.

638 **Baseline clinic visit (Day 1):** Participants in the UK were mailed a pre-visit study pack with a stool
639 collection kit and a health and lifestyle (amended Twins Research health and lifestyle questionnaire
640 ⁴²and food frequency questionnaire (European Prospective Investigation into Cancer and Nutrition

641 (EPIC) Food-Frequency Questionnaire (FFQ)⁴³). In the US, minor modifications were made to the
642 health and lifestyle questionnaires to conform to a US population and the Harvard Semi-quantitative
643 FFQ, a validated US instrument, was substituted for the EPIC FFQ. Stool collection and
644 questionnaires were completed at home and returned to study staff at the baseline visit.

645 Participants were asked to refrain from exercise and to limit fat, fiber and alcohol intake for 24 hours
646 beforehand and to abstain from caffeine from 6pm the night before the baseline visit. Participants
647 arrived at 8:30am for their visit, having fasted from 9pm the night before, and were cannulated in
648 the forearm (antecubital vein) to collect a fasted blood sample, before being fitted with wearable
649 devices (continuous glucose monitor (CGM; Freestyle Libre Pro, Abbott, Abbott Park, IL, US) and
650 wrist-based triaxial accelerometer (AX3, Axivity, Newcastle, UK)). Heart rate and blood pressure
651 were measured using an automated blood pressure monitor while fasted (in triplicate, with mean of
652 second and third measurements recorded). Participant weight, height, hip and waist circumference
653 were measured using standard clinical techniques. Fasting blood glucose level was checked using
654 HemoCue Glucose 201 + System (Radiometer, Crawley, UK) or Stat Strip (Nova Biomedical, Waltham,
655 MA, US) in the UK and US, respectively.

656 Following the baseline blood draw, participants consumed a breakfast (muffins and milkshake at 0
657 min) and lunch (muffins at 240 min) test meal (**Supplemental Table 2**), each to be consumed within
658 10 minutes. Additional venous blood was collected via cannula at 15, 30, 60, 120, 180, 240, 270, 300
659 and 360 minutes. Participants had access to water to sip throughout the visit. Between blood
660 sampling, participants were trained in how to complete the study at home, including when and how
661 to consume standardised test meals, perform DBS, and use the Zoe study app. Upon completing
662 their baseline visit, participants received all the components necessary to complete the home-phase.

663

664 **Home-phase (Days 2-14):** During the study home-phase, participants consumed multiple
665 standardised test meals for breakfast and lunch over a 9-11-day period, differing in macronutrient
666 composition (carbohydrate, fat, protein and fiber) while wearing the CGM and accelerometer.

667 Participants recorded all of their dietary intake and exercise on the Zoe study app throughout the
668 study. DBS tests were completed on 4 days before and after test meals, as outlined in the online
669 protocol⁴¹. Following completion of the home-phase, participants returned all study samples and
670 devices to study staff via standard mail.

671

672 Test meal preparation, nutrient composition, timings and standardised participant test meal
673 instructions

674 Upon completing their baseline visit, participants received a home-phase meal pack containing test
675 meal components (nutrient composition; **Supplemental Table 2**) which they consumed according to
676 standardised instructions for breakfast and, on some days, lunch. Test meals consisted of either an
677 oral glucose tolerance test (OGTT; on 2 days) or muffins, which were consumed on their own or
678 paired with chocolate milk, protein shake, or commercial fiber bars and ordered according to one of
679 3 protocol groups described in **Supplemental Table 2**. Meal order for the 3 protocol groups was
680 randomised using Microsoft Access for each participant, using a 2-block randomisation and 1 non-
681 randomised block.

682

683 Participants were instructed to fast for a minimum of 8 hours prior to consuming a test breakfast
684 meal, and to fast for 3 or 4 hours after meal consumption (depending on test meal; in protocol 1,
685 fasting period was 3 hours for Meal 5 and 4 hours for all other meals; in protocols 2 and 3, the
686 fasting period was 3 hours for all breakfast meals, excluding combinations of breakfast and lunch,
687 where fasting periods were 4 and 2 hours, respectively). They were advised to limit exercise and
688 drink only plain, still water during fasting periods. When fasting was completed, participants could
689 eat, drink and exercise as they liked for the rest of the day. Participants were asked to consume all
690 muffin-based meals within 10 minutes and the OGTT within 5 minutes and to notify study staff if this
691 was not achieved, in which case the data was excluded from analysis. If the participant chose to
692 accompany their home-phase muffin-based test meals with a tea or coffee (with up to 40ml of 0.1%

693 fat cow's milk, but no sugar or sweeteners), they were instructed to consume this drink consistently,
694 in the same strength and amount, alongside all muffin-based test meals throughout the study.
695 Participants were instructed to not consume any food or drink other than water alongside the OGTT,
696 and to avoid physical activity during the 3-hour fasting period that followed it.

697

698 Test meals and any dietary intake consumed within fasting periods, including accompanying drinks,
699 were recorded in the Zoe app by participants with the exact time at consumption and ingredient
700 quantities so that compliance could be monitored by study staff. Only test meals that were
701 completed according to instructions were included in analysis.

702

703 Test meals were prepared and packaged in the Dietetics Kitchen (Department of Nutritional
704 Sciences, King's College London, London, UK) using standard ingredients; plain flour, sugar, baking
705 powder, vanilla essence, milk, egg, salt, high-oleic sunflower oil, whey protein powder, chocolate
706 milkshake powder (Nesquik, Nestle, Gatwick, UK), and commercially available fiber bars (Chocolate
707 Fudge Brownie, Fiber One, General Mills, MN, US; Goodness Bar Apple & Walnut, The Food Doctor,
708 Hesse, UK). Test meals were shipped frozen, under temperature controlled conditions, to the US to
709 limit variability of the intervention. Participants were instructed to freeze their muffins at home and
710 defrost each set of muffins in the fridge the night before consuming them. Test meal drinks were
711 prepared by the participant at home by mixing pre-portioned powder sachets with long-life milk
712 provided (Meal 1, 220ml 0.1% fat milk; Meal 8, 200ml 1.6% fat milk). Powder sachets and fiber bars
713 were stored at room temperature until consumption. The OGTT (Meal 5) consisted of a pre-
714 portioned powdered glucose sachet which participants mixed with 300ml water in the UK. In the US
715 participants were provided with pre-mixed OGTTs ready for consumption (Cat# 82028-512; VRW,
716 US).

717

718 Zoe study app and dietary assessment methodology

719 The Zoe app was developed to support the PREDICT 1 study by serving as an electronic notebook of
720 study tasks, a tool for recording all dietary intake and a portal for communication with study staff.

721 The app sent participants notifications and reminders to complete tasks at certain time-points, such
722 as when their test lunch meals and DBS were due, and asked participants to report their hunger and
723 alertness levels on visual analogue scales truncated from Flint *et al*⁴⁴. Participants were asked to log
724 in the app any exercise which would not be well captured by a wrist-affixed accelerometer, such as
725 cycling. Participants logged their full dietary intake using the app over the 14-day study period,
726 including all standardized test meals and free-living foods, beverages (including water) and
727 medications. Data logged into the app was uploaded onto a digital dashboard in real time and
728 reviewed and assessed for logging accuracy and study guideline compliance by study staff.

729 `Study staff trained all participants at their baseline clinic visit on how to accurately weigh and
730 record dietary intake through the Zoe study app, using photographs, product barcodes, product-
731 specific portion sizes, and digital scales. Study nutritionists also reviewed food logging data by
732 comparing the photographs uploaded by subjects with the items they logged on the app. Any
733 uncertainties were clarified actively with the participant through the app messaging system or via
734 phone while the participant was on the study.

735

736 Protocol versions and amendments

737 Protocol amendments for the PREDICT study, post-commencement of the study and participant
738 enrolment, are as follows: The first amendment (approved by UK IRAS 1st August 2018) allowed
739 additional test meals to be included in the home-phase and participants' logging of gut transit
740 time by using a Metabolic Challenge Breakfast (Meal 1) on the clinic day dyed blue with food
741 coloring. The DBS protocol was also changed according to physiological peaks in biomarkers
742 (triglyceride or C-peptide). Starting on 28 Aug 2018, triglyceride was measured on Days 2-3 at
743 fasting, 300 and 360 minutes post-prandially, while C-peptide was quantified on Days 4-5 at

744 fasting, 30 and 120 minutes post-prandially as described for Protocol Group 2. A second saliva
745 sample collection was also added on the clinic day, at 30 minutes after the metabolic challenge
746 breakfast, to measure salivary amylase production post prandially and provide a comparison to
747 fasted amylase levels. The second amendment (approved by UK IRAS 2nd September 2018) was
748 a change in the lower BMI limit for eligibility to 16.5kg/m² (originally 20 kg/m²). Minor meal
749 changes were made, not requiring ethical approval, which resulted in Protocol Group 3
750 (implemented in January 2019). In the US, on 3 January 2019, the IRB approved an amendment
751 (PREDICT-US v2.0) to address meal changes introduced in the UK for Group 3 and to allow the
752 use of multiple CGMs on the same participant. No other major amendments to the intervention
753 protocol were made during the study period in the US.

754

755 **Outcome variables and sample collection, handling and analysis**

756 **Dried blood spot collection, method validation and analysis.**

757 Dried blood spot collection: Triglyceride and C-peptide were quantified from DBS tests completed by
758 participants at the baseline visit (at fasted baseline and 300 minutes post-breakfast; for method
759 validation) and on the first 4 days of the home-phase while consuming test meals (test timings and
760 associated meals are outlined in the online protocol ⁴¹).

761

762 The Zoe app sent participants reminders to complete their DBS tests at due times, which participants
763 then logged in the app by recording the time at testing and a photo of the completed card for quality
764 assessment by study staff. Test cards not meeting the quality protocol (multiple small spots or
765 inadequate coverage) were not included in analysis. Test cards were stored in aluminium sachets
766 with desiccant once completed and placed in the fridge at the end of the study day or until
767 participants mailed them back to the study site. DBS cards were then frozen (-80 °C) and shipped for
768 analysis (Vitas Analytical Services, Oslo, Norway).

769

770 Dried blood spot method validation: DBS C-peptide and triglyceride concentrations were validated
771 during PREDICT, against venous serum concentrations collected during the baseline clinic visit at 0
772 and 300 minutes post breakfast test meals. Correlations between the two methods were found to be
773 high; for triglyceride (1,772 pairs) Pearson's $r=0.94$; for C-peptide (1,679 pairs) Pearson's $r=0.91$.

774

775 Quantification of total triglyceride from DBS: From the DBS sample, 2 punches were taken and
776 transferred into a HPLC vial and lipids extracted with methanol at 600 rpm and 25 °C for 3 hours. The
777 resulting extract was processed with a triglyceride kit (FUJIFILM Wako Chemicals GmbH, Neuss,
778 Germany) at 600 rpm and 37 °C for 2.5 hours and the reaction products were subsequently analyzed
779 by HPLC-UV. HPLC was performed with a HP 1260/1290 infinity liquid chromatograph (Agilent
780 Technologies, Palo Alto, CA, US) using UV detection. The analyte was separated from matrix
781 components on a 4.6 mm x 100 mm reversed phase column at 40 °C. A one-point calibration curve
782 was made from analysis of triglyceride standard after enzymatic reaction with the kit. The analytical
783 method is linear from 0.5-6 mmol/L with a quantification limit of 0.3 mmol/L.

784

785 Quantification of C-peptide from DBS: C-peptide in DBS were assayed using a Mercodia solid phase
786 two-site enzyme immunoassay (ELISA; Mercodia AB, Uppsala, Sweden). Three spots were punched
787 into the kit plate with anti-C-peptide antibodies bound to the well. Assay buffers were added and C-
788 peptide extracted from the spots at 4 °C. After washing, peroxidase-conjugated anti-C-peptide
789 antibodies were added and after the second incubation and a washing step, the bound conjugate
790 was detected by reaction with 3,3',5,5'-tetramethylbenzidine (TMB). The reaction was stopped by
791 adding acid to give a colorimetric endpoint that was read spectrophotometrically at 450 nm.

792 Stool sample collection, method validation and microbial analysis

793 Stool sample collection: Participants collected a stool sample at home prior to their clinical visit.
794 Samples were collected using the EasySampler collection kit (ALPCO, NH, US) into fecal collection
795 tubes containing DNA/RNA Shield buffer (Zymo Research, CA, US). Upon receipt in the laboratory,
796 samples were homogenised, aliquoted and stored at -80 °C in Qiagen PowerBeads 1.5 mL tubes
797 (Qiagen, Germany). The sample collection procedure was tested and validated internally comparing
798 different storage conditions (fresh, frozen, buffer), different DNA extraction kits (PowerSoilPro,
799 FastDNA, ProtocolQ, Zymo), and different sequencing technologies (16S rRNA and arrays), data not
800 shown.

801

802 Microbiome 16S rRNA gene sequencing and analysis: The DNA was isolated by QIAGEN Genomic
803 Services using DNeasy® 96 PowerSoil® Pro. Optical density measurement was done using
804 Spectrophotometer Quantification (Tecan Infinite 200). The V4 hyper-variable region of the 16S
805 rRNA gene was then amplified at Genomescan, Leiden, Netherlands. Libraries were sequenced for
806 300 bp paired-end reads using the Illumina NovaSeq6000 platform. In total, 9.6 Pbp were generated
807 and raw reads were rarefied to 360k reads per sample. Rarefied reads were analyzed using the
808 DADA2 pipeline ⁴⁵. Quality control of the reads was performed using the "filterAndTrim" function
809 from the DADA2 package truncating eight nucleotides from each read to remove barcodes,
810 discarding all reads with quality less than 20, discarding all reads with at least one N, and removing
811 the phiX Illumina spike-in. Only paired-end reads with at least 120 bp and with an expected DADA2
812 error less than 4 were retained for downstream analyses. Error rates were inferred from the cleaned
813 set of reads ("learnErrors" function) and used in the DADA2 algorithm ("mergePairs" function) for
814 merging the reads, after dereplication ("derepFastq" function). Merged reads were further
815 processed retaining only reads within 280 and 290 bp, representing the majority of the distribution
816 of the lengths. Reads were further processed to remove chimeras using the "removeBimeraDenovo"
817 function with a consensus method. Finally, taxonomy was assigned using the SILVA database

818 (version 132) using the "assignTaxonomy" function and requiring a minimum bootstrap value of 80
819 obtaining a table of relative abundances of operational taxonomic units (OTUs). To address the issue
820 of compositionality in the microbiome data set⁴⁶ the relative abundance values were normalized
821 using the (arcsin-sqrt) transformation as described in ⁴⁷. Measures of alpha diversity were computed
822 (see⁴⁷). The distributions of the Simpson and Shannon indices of alpha diversity on the transformed
823 16S abundance data are presented in **Supplemental Table 4**.

824

825 Venous blood sample collection

826 Participants came into the clinical research facilities at 8:30am and were cannulated in the forearm
827 antecubital vein. Venous blood was collected at 0 minutes (prior to a test breakfast) and at 9 time-
828 points postprandially (15, 30, 60, 120, 180, 240, 270, 300, and 360 minutes). Plasma glucose was
829 analyzed from blood samples collected into fluoride oxalate tubes and centrifuged at 1900 *g* for 10
830 min at 4 °C. Serum C-peptide, insulin, triglyceride, fasting lipid profile, thyroid stimulating hormone,
831 alanine aminotransferase, and liver function panel were analyzed from blood samples collected into
832 gel separator serum tubes and allowed to stand at room temperature before centrifuging at 1900 *g*
833 for 10 min at 4 °C. Samples were aliquoted and stored at -80 °C. Blood, for complete blood count
834 (CBC) analysis, was collected into EDTA tubes, kept at 4 °C and analyzed within 12 hours of
835 collection.

836

837 Serum biomarkers

838 In the UK, insulin, glucose, triglyceride and C-peptide analysis was conducted by Affinity Biomarkers
839 Labs (London, UK). Glucose and triglyceride analyses were conducted on a Siemens ADVIA 1800
840 using Siemens assay kits (Siemens Healthcare Diagnostics Ltd, Surrey, UK). Triglyceride was analyzed
841 using the ADVIA chemistry triglyceride method based on the Fossati three-step enzymatic reaction
842 with a Trinder endpoint. Glucose was analyzed using the ADVIA chemistry glucose oxidase (GLUO)

843 method (based on the modified method of Keston). C-peptide and insulin were analyzed using the
844 Siemens ADVIA Centaur XP systems using a two-site sandwich immunoassay. Complete blood count
845 (CBC) was measured by Viapath (London, UK) for the UK cohort using standard automated clinical
846 chemistry techniques. The inter-assay coefficient of variation for PREDICT samples analyzed by
847 Affinity were: insulin 3.4%, C-peptide 7.9%, triglyceride 3.7%, and glucose 2.6%.

848 In the US, CBC was established using fresh blood samples in the MGH Core Laboratory. Hb1AC tests
849 were performed by the MGH Diabetes A1c lab. Glucose, insulin, triglyceride, and C-peptide were
850 conducted by Quest Diagnostics (Boston, MA) using standard automated clinical chemistry
851 techniques.

852 Upon completion of the US study, frozen serum and plasma samples were sent from the US to the
853 UK and the entire cohort had liver function panel, full lipids (TC, HDL-C LDL-C and triglyceride),
854 thyroid stimulating hormone and alanine aminotransferase measurements performed by Affinity
855 Biomarkers Labs. Details described elsewhere ⁴⁸.

856

857 **Glucose using continuous glucose monitoring**

858 Interstitial glucose was measured every 15 minutes using Freestyle Libre Pro continuous glucose
859 monitors (Abbott, Abbott Park, IL, US). Monitors were fitted by trained nurses on the upper, non-
860 dominant arm at participants' baseline visit and covered with Opsite Flexifix adhesive film (Smith &
861 Nephew Medical Ltd, Hull, England) for improved durability, and worn for the entire study duration
862 (14 days). Data collected 12 hours and onwards after activating the device was used for analysis. For
863 a subgroup of participants (n=377), we fitted two monitors on their arms and calculated the
864 Coefficient of Variation (CV =11.75%) and correlation ($r = 0.97$) of their iAUC responses to
865 standardized meals (**Extended Data Figure 2b**).

866

867 Time points for analyses:

868 *Glucose:* The 2-hour glucose iAUC was used for both clinic and at-home analyses.

869 *Insulin and C-peptide:* C-peptide was measured at home as a surrogate for insulin secretion,
870 because the reliability of C-peptide measured from DBS is higher than that of insulin (see⁴⁹) and C-
871 peptide remains stable on paper filters for up to 6 months⁴⁹. C-peptide was measured at 60 minutes
872 postprandially to coincide with the peak in C-peptide seen in healthy individuals in clinic, and again
873 at 120 minutes to coincide with the strong decline in insulin level (**Extended Data Figure 2c**).
874 However, because previous genetic studies have tested the heritability of postprandial insulin at 120
875 minutes, this time point was included for our own heritability analyses (**Figures 2b-c**). All other
876 analyses refer to the 1-hour rise for C-peptide.

877

878 *Triglyceride:* The rise in triglyceride at 6 hours postprandially (triglyceride_{6h-rise}) was selected to
879 represent postprandial lipemic response from serum collected at clinic and home-based DBS tests.
880 This is a measure of lipemia most closely correlated with atherogenic lipoproteins compared to
881 iAUC_{0-6h}C and 4h triglyceride concentration (see.⁵⁰⁻⁵²

882

883 Activity and sleep

884 Energy expenditure was measured using a triaxial accelerometer (AX3, Axivity, UK) fitted by nurses
885 at the baseline visit on the non-dominant wrist and worn for the duration of the study (except
886 during water-based activities, including showers and swimming). Accelerometers were programmed
887 to measure acceleration at 50 Hz with a dynamic range of ± 8 g (where g refers to local gravitational
888 force equal to 9.8 m/s^2). Non-wear periods were defined as windows of at least 1 hour with less than
889 13mg for at least 2 out of 3 axes, or where 2 out of 3 axes measured less than 50mg. Windows of
890 sleep were measured using methods described elsewhere⁵³.

891

892 Genotyping

893 Whole genome genotyping was available for 241 individuals from the UK cohort from previous
894 TwinsUK studies. Genotyping was performed with the Illumina Infinium HumanHap610. Normalised
895 GWAS intensity data were pooled and genotypes called on the basis of the Illuminus algorithm. No
896 calls were assigned if the most likely call was less than a posterior probability of 0.95. Validation of
897 pooling was done by visual inspection of 100 random, shared SNPs for overt batch effects (none
898 were observed). SNPs that had a low call rate ($\leq 90\%$), Hardy-Weinberg p values $< 10^{-6}$ and minor
899 allele frequencies $< 1\%$ were excluded, and samples with call rates $< 95\%$ were removed. Genotype
900 imputations were performed to increase the coverage. Imputation of genotypes for all polymorphic
901 SNPs that passed the quality control stage were performed on the Michigan Imputation Server
902 (<https://imputationserver.sph.umich.edu>) using the 1000G Phase3 v5 reference panel⁵⁴. SNPs
903 previously reported to be associated with postprandial glycemia, triglyceride or insulin *GWAS*¹⁷⁻²⁰
904 were extracted from the full set of genome wide genotypes using PLINK and tested for association
905 with postprandial measures using linear regression methods.

906 Processing of habitual diet information

907 UK nutrient intakes were determined using FETA software to calculate macro- and micro- nutrient
908 data⁴³. Submitted FFQs were excluded if greater than 10 food items were left unanswered, or if the
909 total energy intake estimate derived from FFQ as a ratio of the subject's estimated basal metabolic
910 rate (determined by the Harris-Benedict equation)⁴³ was more than two standard deviations outside
911 the mean of this ratio (< 0.52 or > 2.58).

912

913 **Statistical analysis**

914 **Basic analyses**

915 The descriptive characteristics of study participants are summarized in **Supplemental Table 1**

916 In order to reduce the dimension of the data, principal component analysis (PCAs) with orthogonal
917 transformation (varimax procedure) was applied to derive principal components (PC) representative
918 of individual characteristics (20 PCAs), microbiome (40 PCAs), meal composition (1 PCA), habitual
919 diet (5 PCAs) and meal context (5 PCAs) (see **Supplemental Table 3** for full list of input variables). All
920 the necessary prerequisites of PC analysis including linearity, Kaiser–Meyer–Olkin measure of 0.88,
921 and the significant Bartlett’s test of sphericity ($p < 0.001$) were met. Each participant received a
922 score for each category mentioned above. To investigate the association between each outcome
923 (iAUC, triglyceride_{0h-rise}, C-peptide_{1h-rise}) and our exposures (individual baseline characteristics,
924 microbiome (16S), meal content, habitual diet and meal context) multivariable regressions were
925 applied and R^2 reported. Further, we derived PCAs for the anthropometrics, biochemical/clinical
926 factors, physical activity and sleep features separately to investigate their role. Multi-collinearity for
927 the multiple linear regressions was assessed with variance inflation factors (VIF) at each step⁵⁵.
928 Multi-collinearity was considered high when the VIF was $>10^8$. Receiver operating characteristic
929 (ROC) curves were constructed and the area under the curve (AUC) was calculated to assess the
930 discriminatory power of (fasting blood glucose vs. 2h glucose iAUC), (fasting triglyceride vs.
931 triglyceride_{0h-rise}) and (fasting C-peptide vs. C-peptide_{1h-rise}) to detect impaired glucose tolerance, and
932 ASCVD 10 year risk (70% applied as a cut-off point). Values of AUC range from 0.5 and 1, with 0.5
933 indicating no discrimination, and 1 indicating perfect discrimination (2). A p-value ≤ 0.05 was
934 considered statistically significant. All analyses were performed using R (version 3.4.2 R Core Team
935 (2017)).

936 **Meal composition**

937 To estimate macronutrient effects on glycemic response, we fitted a multivariate regression model
938 with carbohydrates, fats, fiber and protein as predictors on meals 1, 2, 4, 5, 6, 7 and 8.

939 Multicollinearity was assessed for these predictors through VIF and we concluded that it was non
940 existent (VIF < 10). The regression coefficients were all significant ($p < 0.001$) with values -79.23
941 mmol/L*s, -142.41 mmol/L*s and -185.49 mmol/L*s for fat, fiber and protein respectively, after
942 having adjusted by carbohydrates.

943 **Heritability and ACE model**

944 To estimate the heritability, we analyzed the data according to the classical ACE model. In this
945 model, heritability is an approximation of the relative importance of additive genetic differences for
946 variance of postprandial responses in the population⁵⁶. Shared or familial environmental influences
947 reflect experiences that contribute to twin similarity. Non-shared or individual-specific
948 environmental influences refer to the contribution of environmental experiences not shared by
949 family members. Information concerning shared genetic and environmental influences is best
950 estimated by structural equation modelling techniques that fit models of twins by zygosity in order
951 to describe the 154 causes of the variance in OA. Therefore, the total variance in the trait can be
952 partitioned into genetic variance (A), shared (familial) environmental variance (C), and individual-
953 specific environmental variance (E). The level of statistical significance was set at $p < 0.05$ in all
954 analyses, and the R software (version 3.0.2) together with the “mets” (Multivariate Event Times)
955 package (<https://rdr.io/cran/mets/src/R/methodstwinlm.R>) was used for all statistical analyses.
956

957 **Meal ranking**

958 Six different type of meals were ranked for each individual as being the one with the highest glucose
959 2h iAUC for that person (rank 6), the one with the second highest glucose iAUC (rank 5).....down the
960 the one with the lowest glucose 2h iAUC (rank 1). The distribution of these “in-person rankings” is
961 presented in **Extended Data Figure 3**.

962

963 **Multilinear ANOVA to assess role of individualized responses to meals**

964 The different sources of variation in glycemc response for Meal 2,3,4,6 and 8 (described in
965 **Supplemental Table 3**) were analysed using the Multilevel Linear ANOVA⁴⁰ model
966 and were analysed using a multilevel (hierarchical) linear Bayesian ANOVA model as described by
967 Gelman and Hill⁵⁷.

968 The different sources of variation in glycemc response for Meal 2,3,4,6 and were analysed using a
969 multilevel (hierarchical) Linear Bayesian ANOVA model as described by (Gelman & Hill 2007).

970

971 Hierarchical Bayes models can accommodate non-normal dependent variables that are difficult to
972 incorporate in classical ANOVA and multilevel linear models . The approach consists of sub-models at
973 two levels: at level 1 the parameters of individuals, meals and person-meal interactions, and at level
974 2 the moments of the distributions from which level 1 parameters are drawn. Level 2 imposes some
975 homogeneity on level 1 parameters, for example

976

977 $a_m \sim N(0, a_a^2)$ i.e. the meal terms are are distributed normally with the same standard deviation
978 a_a , ensuring homogeneity.

979 $a_a \sim HalfCauchy(5)$ i.e. the standard deviation of the above distribution has a particular prior (a
980 half cauchy distribution with a scale factor of 5) -

981 The other terms ($\{\mathcal{Z}_p, y_{m,p}, E_{m,p,k}, E_{m,p,k,n}\}$) have similar hierarchical distributions (though the
982 standard deviations of $E_{m,p,k}, E_{m,p,k,n}$ have uniform prior as opposed to a half cauchy).

983 The parameters at both levels (i.e. all the a_m 's and a_a and analogously for the other parameters)
984 are sampled using an Markov Chain Monte-Carlo routine in pymc3⁵⁸ and we plot the sampled values
985 of $a_a, a_\beta, a_\gamma, a_E$ and a_{E_n} in **Figure 6b**.

$$\log(iAUC) = y_{m,p,k,n} = \alpha_m + \beta_p + \gamma_{m,p} + \epsilon_{m,p,k} + \epsilon_{m,p,k,n}$$

986

987 where:

988 $-\log(iAUC) = y_{m,p,k,n}$: the 2 hour iAUC for person p , eating meal m , for the k th time measured on

989 cgm n (given the availability of data with 2 CGMs for a subset as described in below.

990 the 2 hour iAUC for person p , eating meal m , for the k th time measured on cgm n (given that we

991 have 2 cgms for many people)

992 - a_m : meal content (across all people) for meal m , e.g. high and low carbohydrate meals

993 - $\{\beta_p$: individual glucose scaling (across all meals) for person p , e.g. overall high and low responding

994 people

995 - $y_{m,p}$: the meal-specific response for individual p to meal m , e.g. a specific person responds

996 particularly strongly to a specific meal

997 - $E_{m,p,k,n}$: error stemming from the cgm (participants selected for this analysis wore 2 CGM devices,

998 so n indexes the device providing the measurement)

999 - $E_{m,p,k}$: other sources of variation, including meal timing, exercise, sleep and circadian rhythm

1000 This Bayesian ANOVA model is a Bayesian hierarchical model attempts to explain the observed

1001 $\log(iAUC)$ of a meal as a sum of categorical terms., i.e. individuals are not classified according to any

1002 characteristics but are included as unique individuals with $\log(iAUC)$ 2h glucose) for various different

1003 meals. If this was an extended Glycemic Index model it would correspond to expressing the

1004 $\log(iAUC)$ as the sum of a meal term (analogous to the glycemic load of the meal) and an

1005 individualized term. This “individual glucose scaling” is not a linear function of a person’s

1006 characteristics (such as age, sex or BMI) but rather it is how each individual ranks overall given the

1007 $\log(iAUC)$ values for the various meals. This allowed us to test whether there was an interaction term

1008 between meals and persons, i.e. an individualized response component to particular meals that was

1009 not merely due to a person being a high, average or low responder and to a meal having on average

1010 a higher glycemic response (e.g. OGTT) than another meal (e.g. a high fat muffin). Given the

1011 availability of data concerning repeated occurrences of a person eating a particular meal and
1012 multiple CGMs measurements for the same meal we were able to extend the model to include a
1013 person-meal interaction and a CGM error and, analogously, infer the error due to the CGMs and the
1014 degree to which a person's response to a particular meal is consistently higher or lower than one
1015 would expect from the glycemic index model .i.e. a personalized glycemic load. The person-meal
1016 interaction effects allow different people to have different ordering of glycemic responses to meals,
1017 so one person might respond more strongly to meal A than meal B, whilst another person might
1018 respond more strongly to meal B than meal A. **Figure 6c** shows show 50% and 95% intervals on
1019 standard deviations of the effects in the model. These can be approximately interpreted as percent
1020 increase (or decrease) in iAUC contributed by the various effects in the model.

1021

1022 **CGM repeatability.**

1023 A subset of participants (n=483) wore two continuous glucose measurement devices simultaneously,
1024 providing duplicate measurements for the meals they consumed and therefore allowing us to
1025 distinguish CGM error from unexplained sources of variation. Postprandial glucose measurements
1026 for 3280 meals eaten collectively by 483 participants from UK were used in this analysis. (**Extended**
1027 **Data Figure 2b**).

1028

1029 **Computation of clinical indices**

1030 *Atherosclerotic Cardiovascular Disease 10 year risk:* (AHA/JACC ASCVD 10 year risk) The 10-year
1031 atherosclerotic cardiovascular disease (ASCVD) ⁵⁹ risk score is a gender and race specific single
1032 multivariable risk assessment tool used to estimate the 10-year CVD risk of an individual, and has
1033 clinically replaced the Framingham-10 year cardiovascular risk score. It is based on the age, sex,
1034 ethnicity, total and HDL cholesterol, systolic blood pressure, smoking status, use of blood pressure
1035 lowering medications, and the presence of type 2 diabetes (T2D).

1036 Impaired glucose tolerance: We used the standard definition from the American Diabetes
1037 Association ⁶⁰ (Fasting plasma glucose < 7.0 mmol/l and OGTT 2-hour value >= 7.8 mmol/l but < 11.1
1038 mmol/l).

1039

1040 **Validation of Machine learning model cross validation and difference (Bland-Altman plots)**

1041 To further illustrate the reliability of the machine learning predictions, we conducted a leave-one-
1042 out cross validation procedure and generated Bland-Altman plots to analyze the agreement
1043 between two. To generate the Bland-Altman plots we used the Predict UK and US data showing
1044 Predicted vs Measured postprandial responses. We generated Bland-Altman plots for predicted and
1045 measured postprandial responses for each biomarker (Triglycerides, C-peptide and Glucose).
1046 **(Extended Data Figure 4a).**

1047 **Leave-one-out cross-validated Pearson R scores in Predict UK**

1048 To perform k-fold cross validation, the entire dataset is split into k groups. Treating each group as a
1049 test set and the remaining groups as the training set, the model is fitted k times. The Pearson's R
1050 between the values predicted by the fitted models and the measured values in the test sets is used
1051 as the metric for model evaluation, which we refer to as the cross-validated Pearson-R.

1052

1053 The special case, where k is the size of the dataset, is referred to as leave-one-out cross-validation,
1054 and we refer to the corresponding evaluation metric as leave-one-out cross-validated Pearson R. The
1055 machine learning models for the three biomarkers of interest were evaluated using the
1056 aforementioned metric and are reported in the Extended Data Figure 4b . These scores are similar to
1057 the cross-validated 5-fold scores in the main text.

1058

1059

1060

1061 **Methods References:**

1062

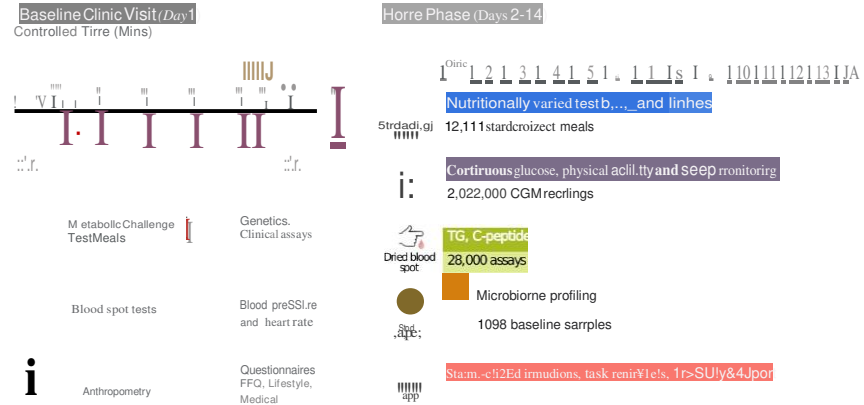
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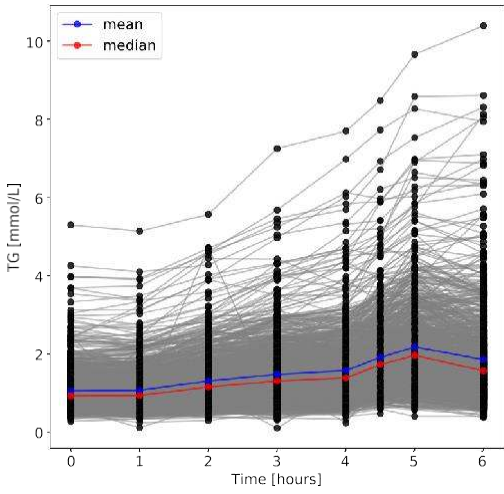
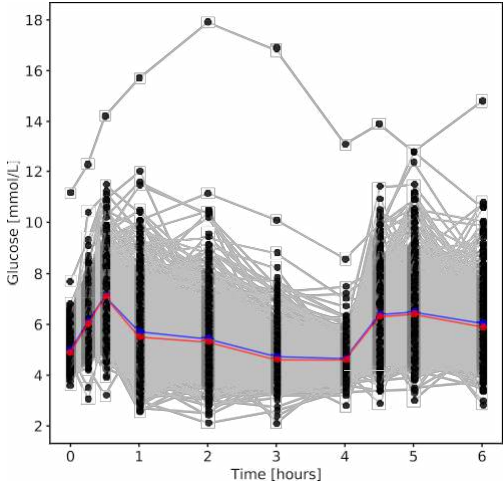
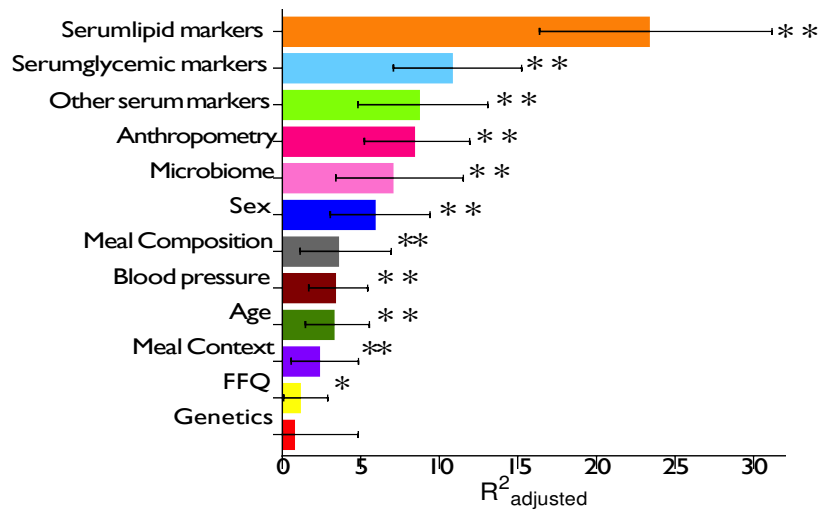
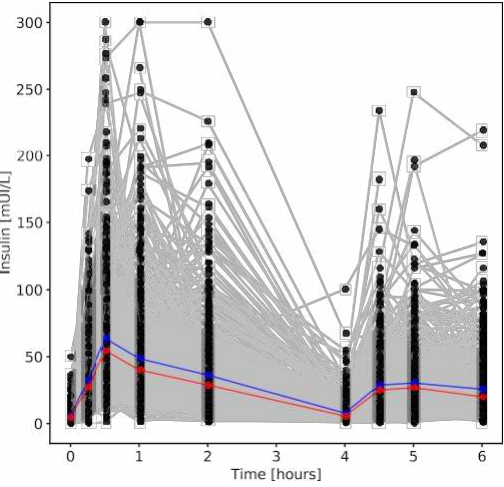
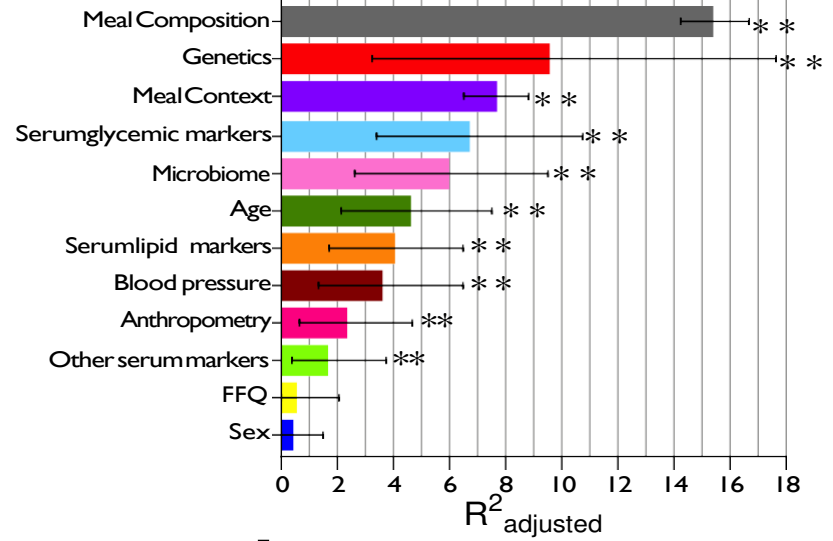
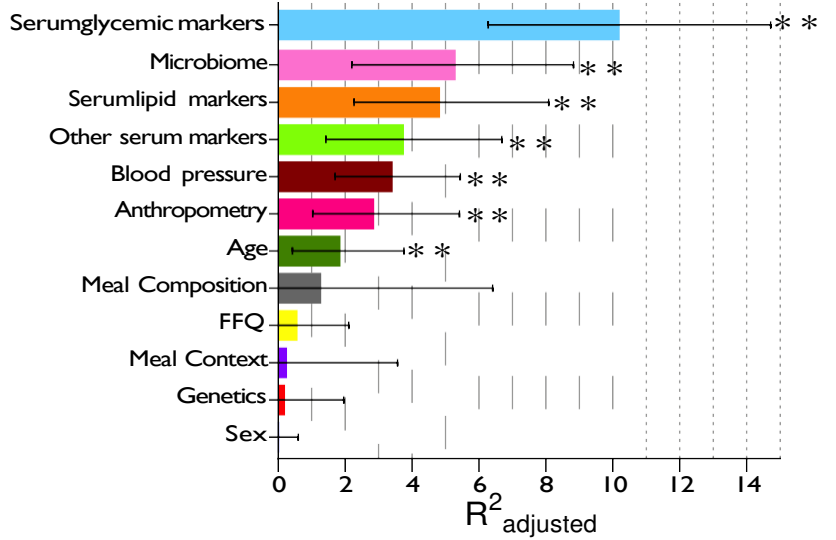
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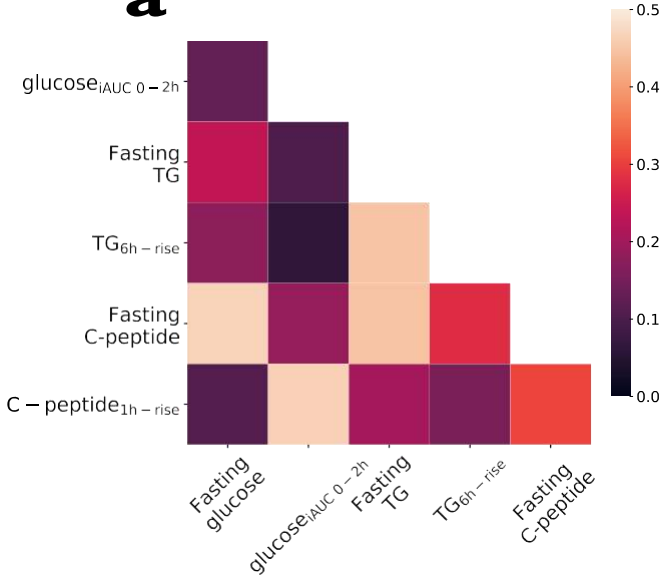
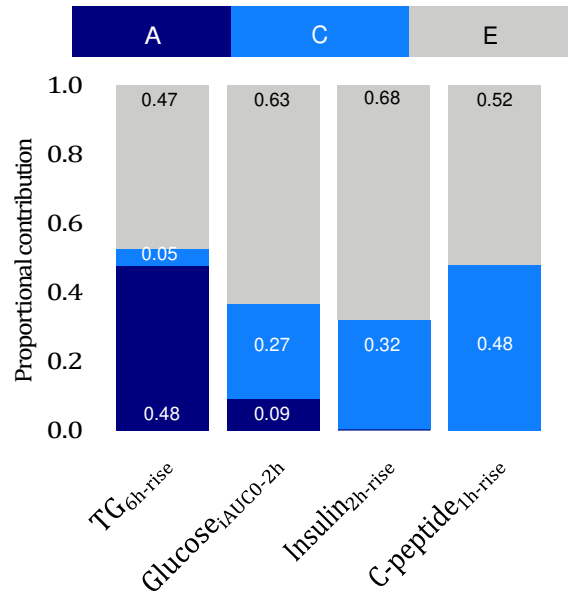
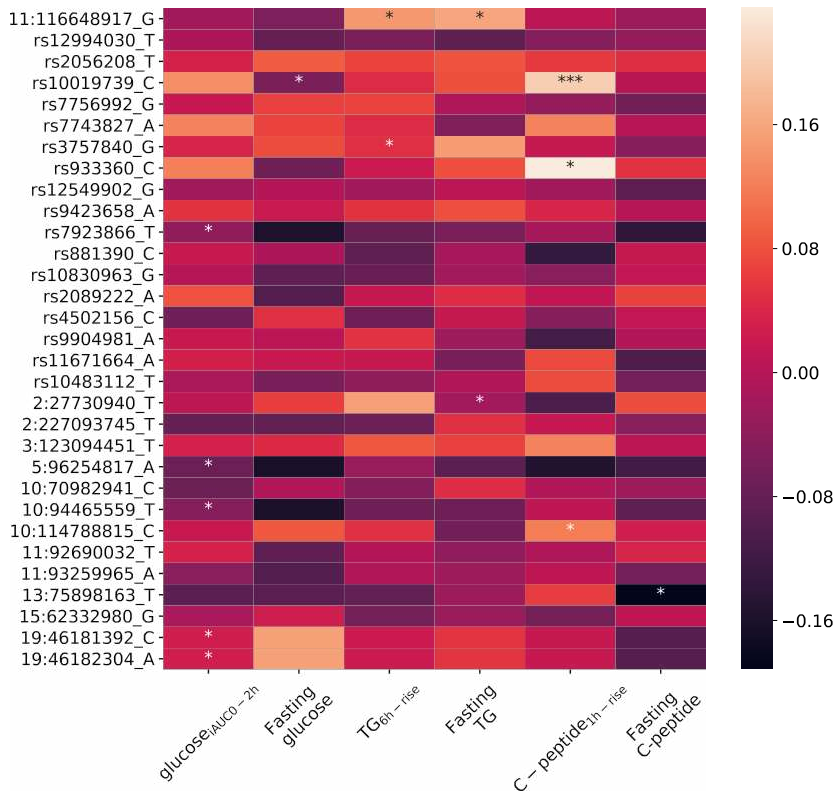
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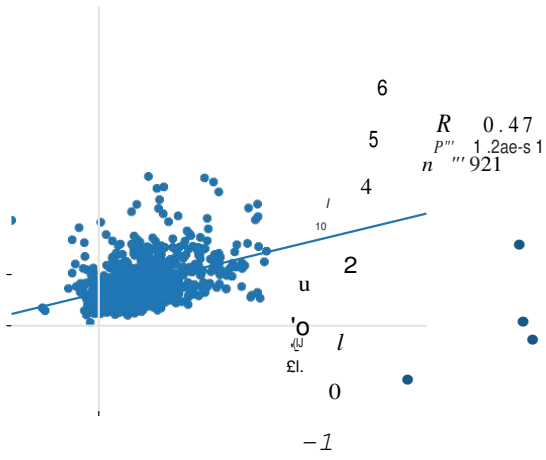
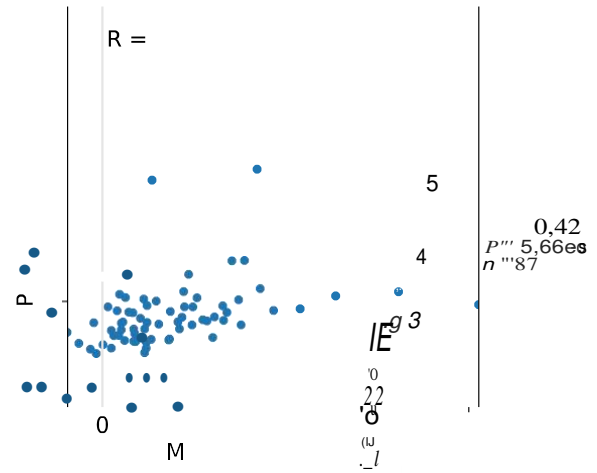
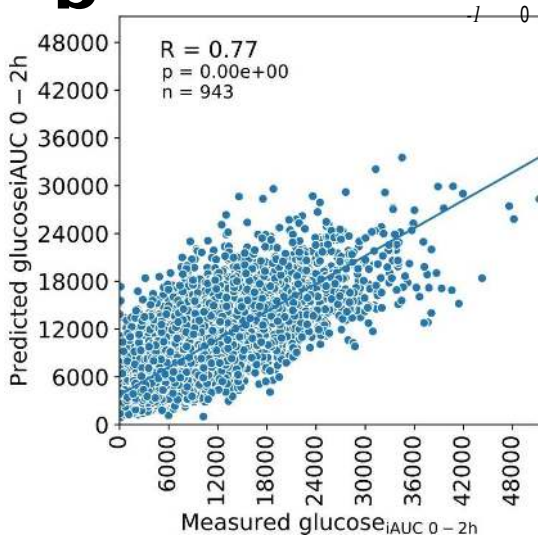
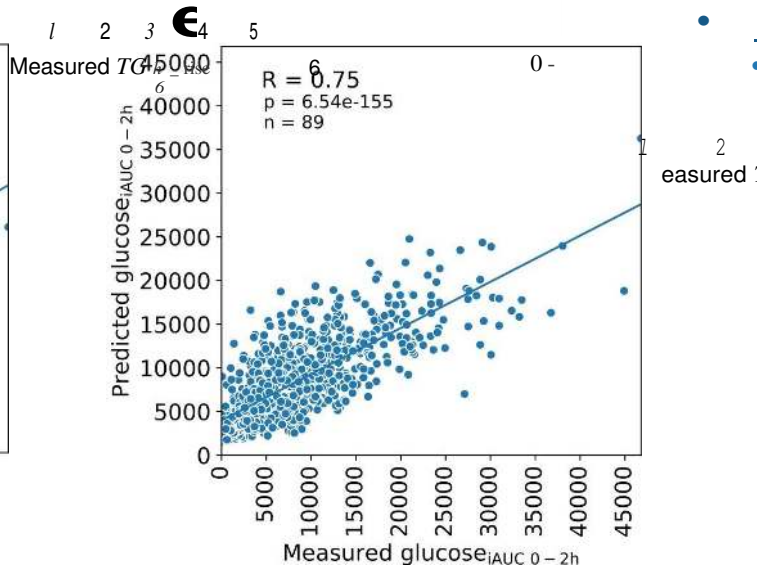
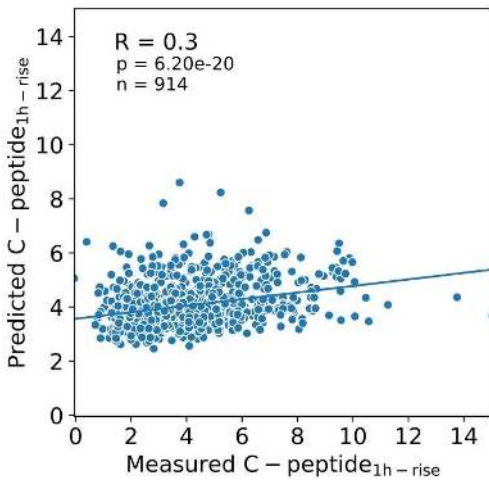
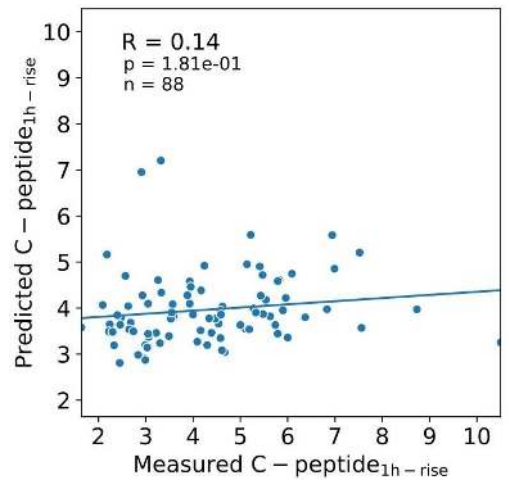
Main Cohort
UK (n=1002)

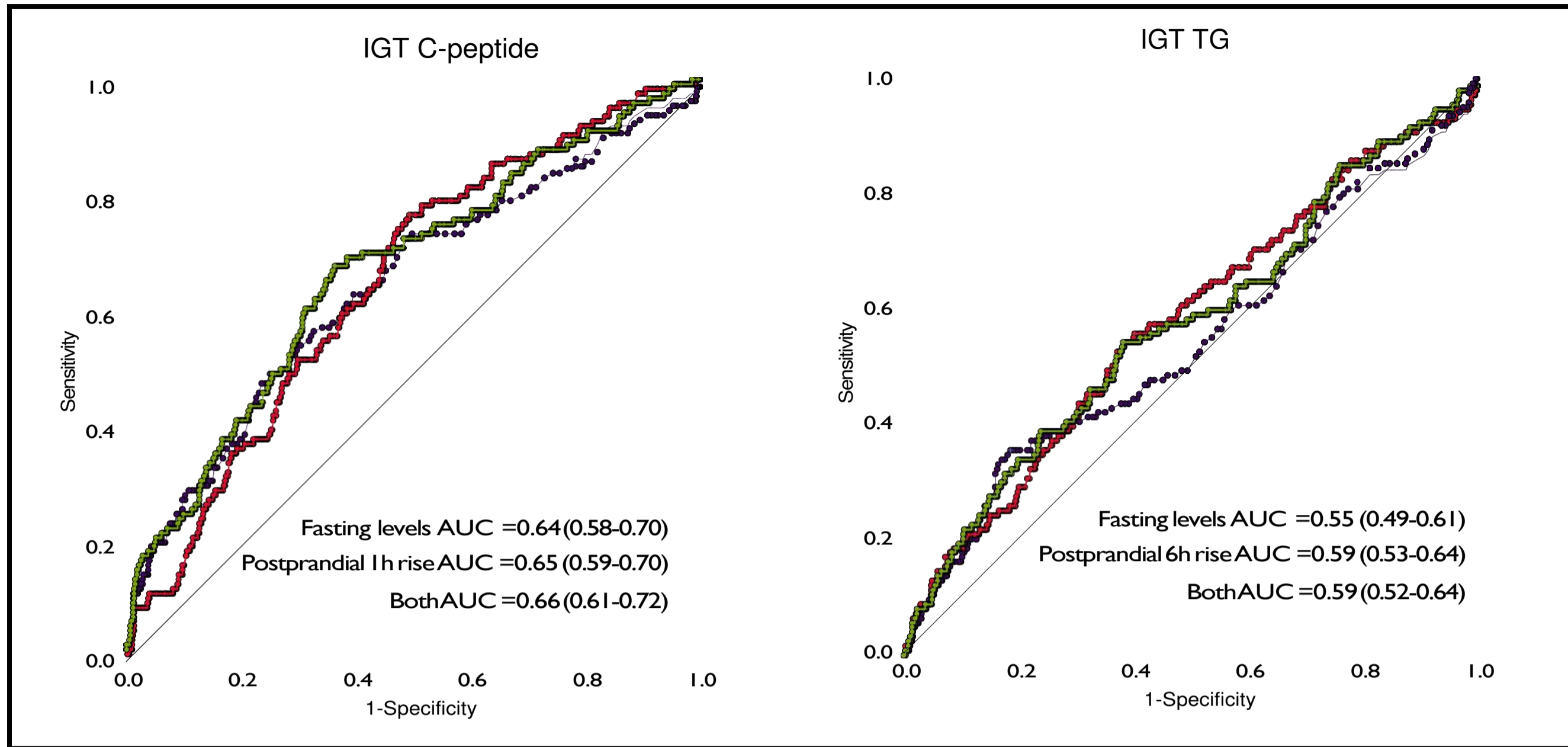
Validation Cohort
US (n=100)



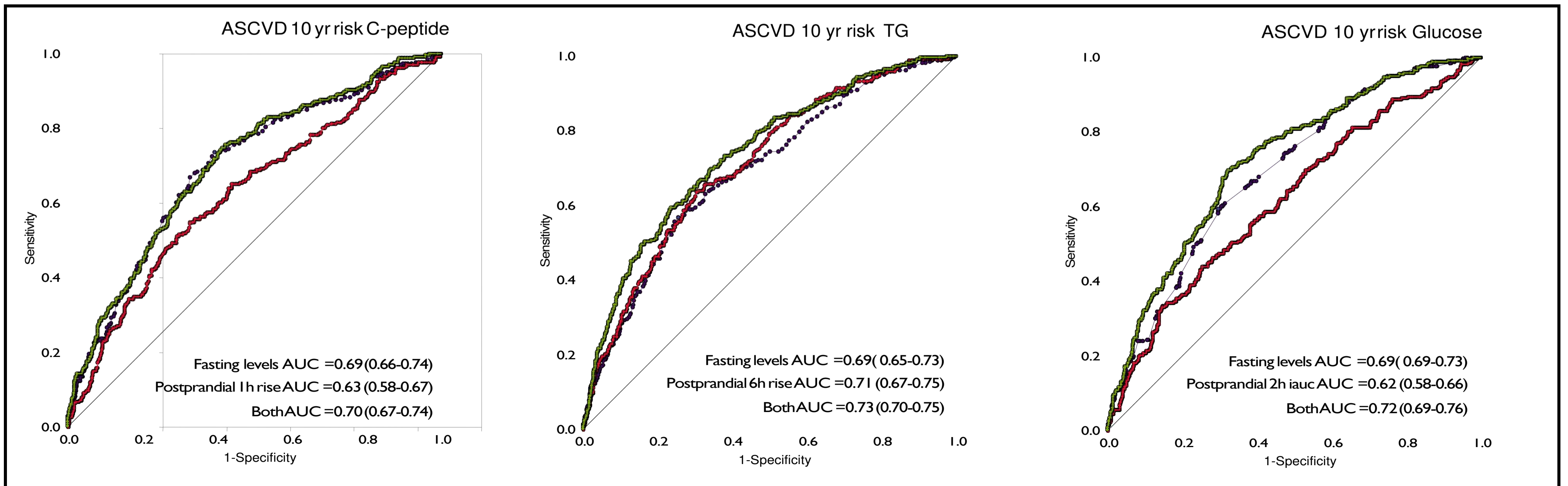
a**b****c****d**

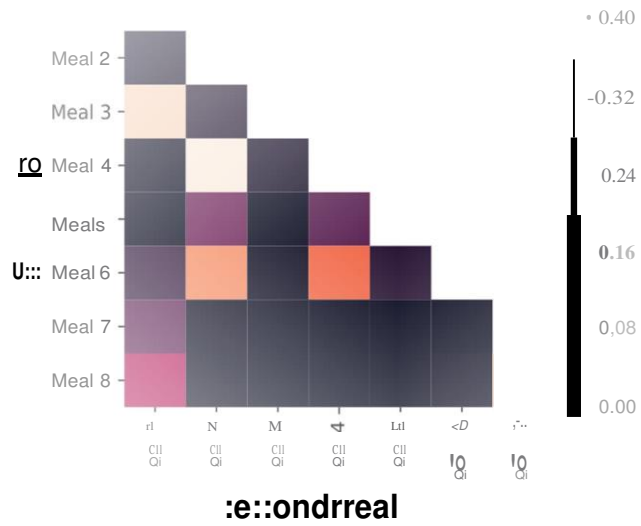
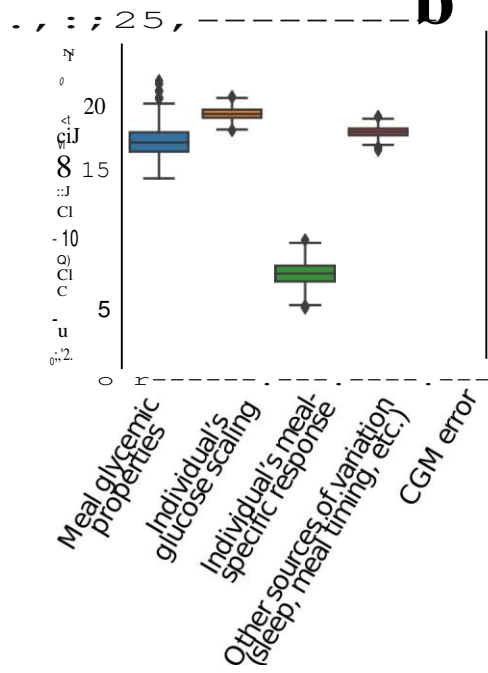
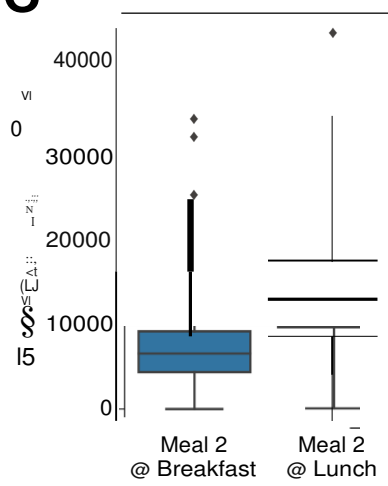
a**b****c**

a**d****b****e****c****f**

a

● fasting
 ● postprandial
 ● both

b

a**b****c**

Extended Data Figure 1. Consort Diagrams for (a) UK and (b) US populations in the PREDICT 1 study.

a

Assessed for eligibility
(n= 1270)

Excluded from enrolment
(n=268)

Enro lled(n=1002)

- Withdrew (n=20)
- Lost to follow-up (n=15)

Successfully completed the
study (n=967)

b

Assessed for eligibility
(n= 355)

Excluded from enrolment
(n=255)

Enrolled(n=100)

- Withdrew (n=4)
- Lost to follow-up (n=1)

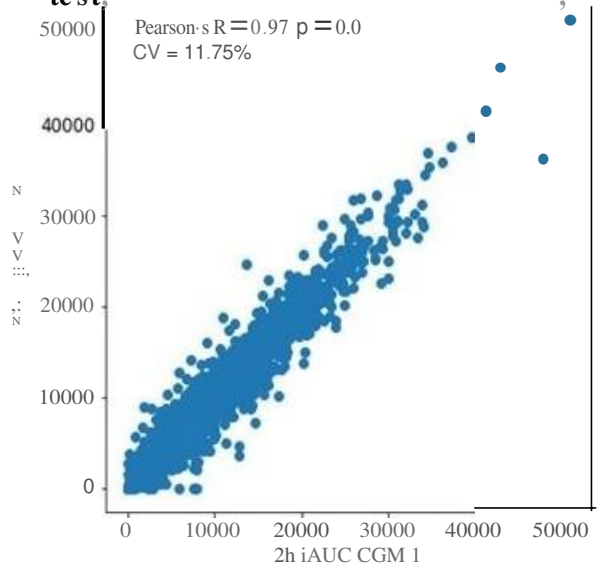
Successfully completed the
study (n=95)

Extended Data Figure 2. Repeatability in the PREDICT 1 study

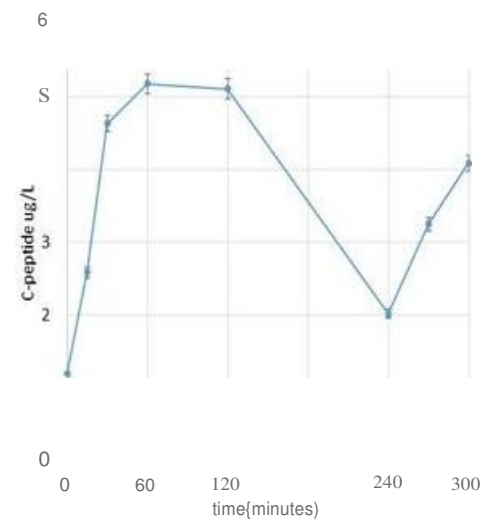
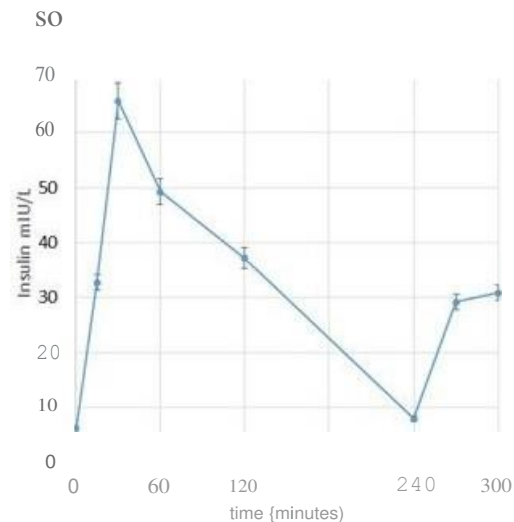
a. Intra-class correlations

Metabolic outcome	num meals	Timepoint/ trait	ICC	95%CI
TG	648	fasting	0.670	0.60 - 0.72
		Sh	0.660	0.60 - 0.72
		6h	0.730	0.68 - 0.78
		fasting-Sh rise	0.410	0.32 - 0.49
		fasting-6h rise	0.460	0.37 - 0.54
2lucose	8038	2h-iAUC	0.74	0.72 - 0.75
c-peptide	626	fasting	0.720	0.66 - 0.77
		0.Sh	0.560	0.47 - 0.64
		2h	0.710	0.64 - 0.76
		fasting-0.S h rise	0.470	0.37 - 0.56
		fasting-2h rise	0.620	0.54 - 0.69

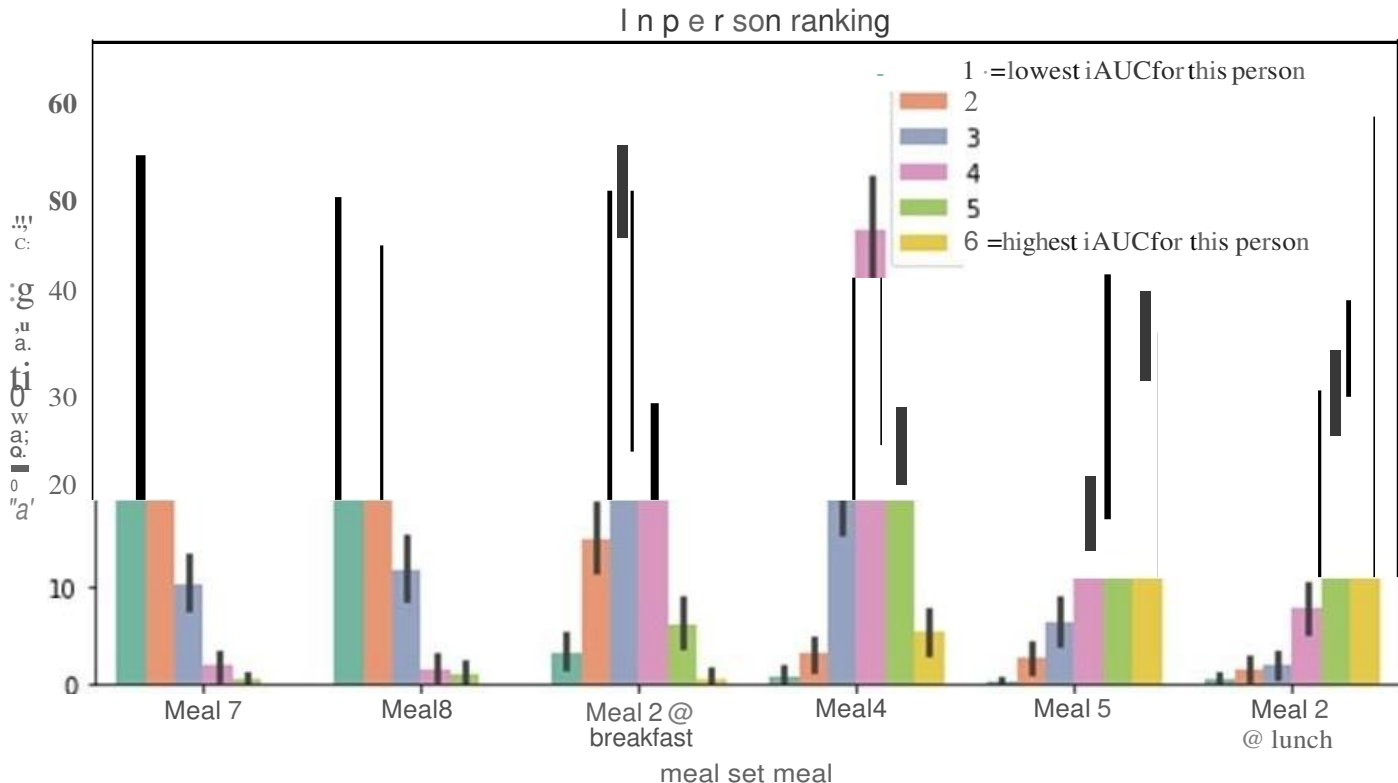
b. Pearson's correlation and CV of 2h-iAUCs measured with two monitors worn by the same participant (n=377). P-value from two-sided test.



c. Mean and standard error of fasting and postprandial serum insulin and C-peptide concentrations during the clinic visit in the PREDICT 1 study, n=1,036.

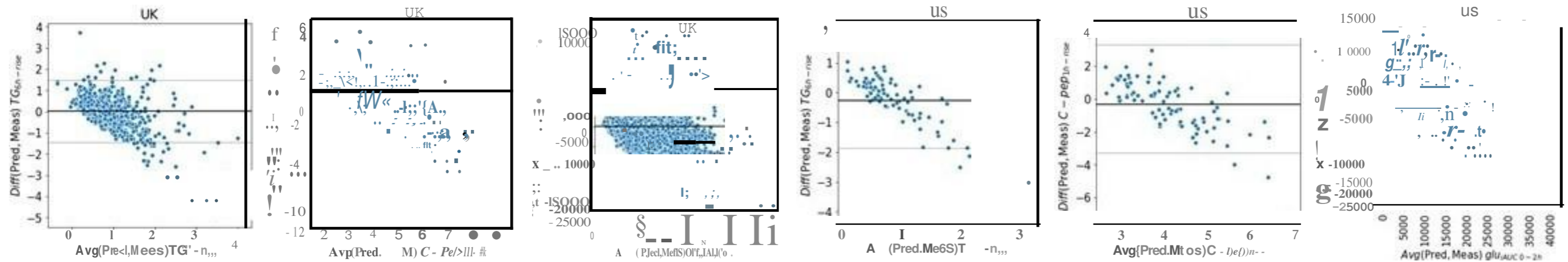


Extended Data Figure 3. Frequency distribution of in-person ranking for 6 of meals shown in Figure 6a (High fat 40g= meal 7, High protein = meal 8, UK average= meal 2, High carb = meal 4, OGTT = meal 5, Uk avgat lunch = meal 2). n=1102 participants



Extended Data Figure 4. Machine Learning comparisons, cross validation and repeatability

a. Bland-Altman plots comparing predicted and measured postprandial responses in TG, glucose and C-peptide using UK and US data. The sample sizes used n=number of meals: triglyceride UK: n=958 US: n=91; C-peptide UK: n=957 US: n=93; Glucose UK: n=1155 US: n=1200



b. Leave-one-out cross-validated Pearson R scores in PREDICT UK. 5-fold cross validation for Triglyceride 6 hour rise on n=958 meals, for Glucose 2h iAUC on n=11550 meals, p-values shown for two-sided t-test

UK data set TG 6h-rise	Glucose iAUC 2h
Leave-one-out 0.49, p = 2.03e-56	0.77, p = 0.0

c. comparison of models using repeat meals vs not using them

individual glucose scaling estimate using all repeat meals :

18.7% change in glucose 2h iAUC 95% CI [17.9-19.5%]

individual using only a single meal from each set (one OGTT, one high carb, one high fat etc).

18.2% change in glucose 2h iAUC 95% CI [17.2-19.2%].

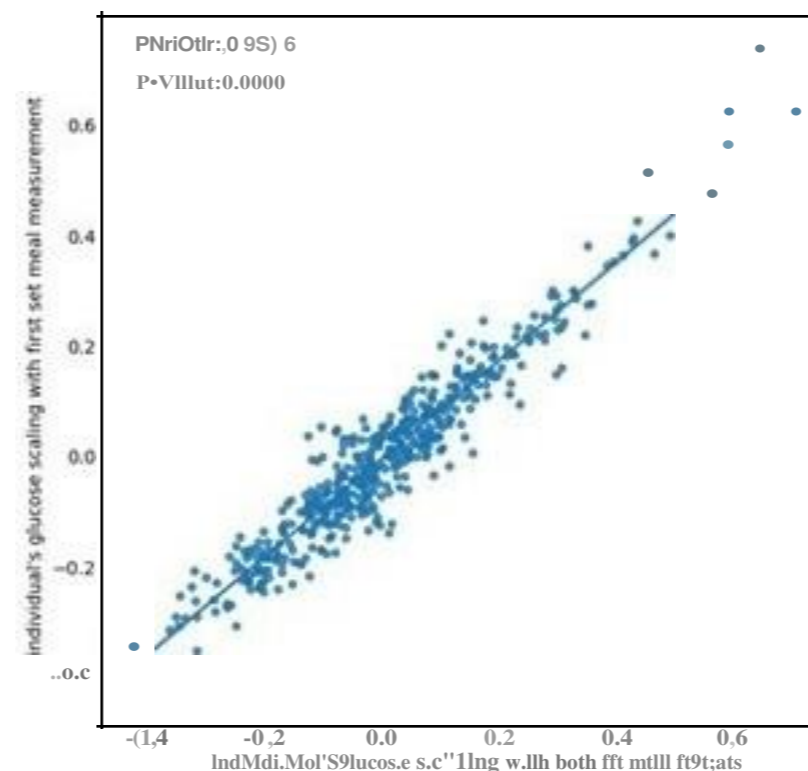


Table number	Title
S Table 1	Study eligibility criteria & descriptive baseline characteristics
S Table 2	Test meal nutritional composition and ordering
S Table 3	Proportion of postprandial response variances explained by individual characteristics
S Table 4	ACE heritability models, SNPs and 16S sequencing
S Table 5	Machine Learning Input Features