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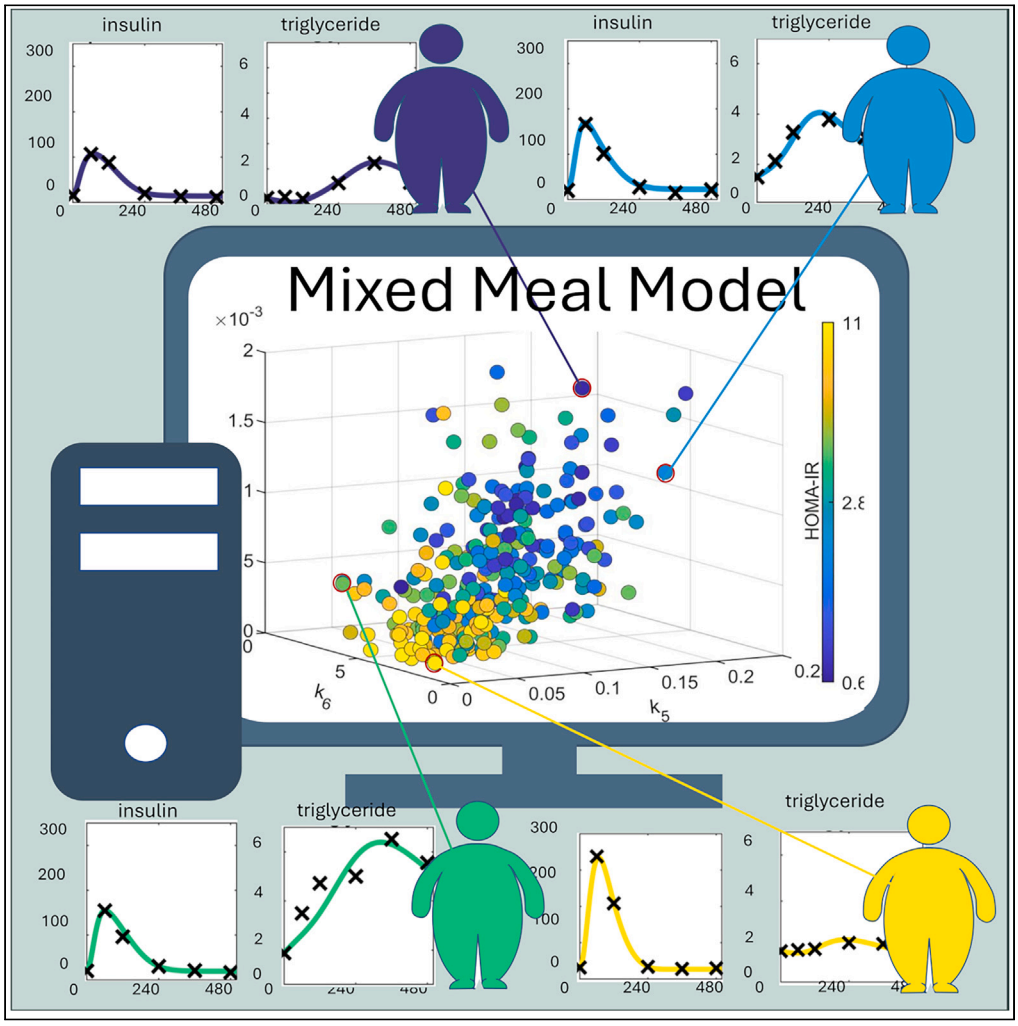

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Highlights

A personalized Meal Model can be generated by fitting to meal response data

The meal model quantifies insulin resistance, β-cell functionality, and liver fat

The model reduces meal data to a three-dimensional measure of metabolic health

Personalized Meal Models reveal changes in metabolic health after an intervention

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Quantifying the effect of nutritional interventions on metabolic resilience using personalized computational models

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SUMMARY

The manifestation of metabolic deteriorations that accompany overweight and obesity can differ greatly between individuals, giving rise to a highly heterogeneous population. This inter-individual variation can impede both the provision and assessment of nutritional interventions as multiple aspects of metabolic health should be considered at once. Here, we apply the Mixed Meal Model, a physiology-based computational model, to characterize an individual's metabolic health *in silico*. A population of 342 personalized models were generated using data for individuals with overweight and obesity from three independent intervention studies, demonstrating a strong relationship between the model-derived metric of insulin resistance ($\rho = 0.67$, $p < 0.05$) and the gold-standard hyperinsulinemic-euglycemic clamp. The model is also shown to quantify liver fat accumulation and β-cell functionality. Moreover, we show that personalized Mixed Meal Models can be used to evaluate the impact of a dietary intervention on multiple aspects of metabolic health at the individual level.

INTRODUCTION

Overweight and obesity have been associated with an increased risk for the development of non-communicable cardiometabolic diseases, which are among the leading causes of mortality worldwide.[1–3] The increase in adipose tissue mass in overweight and obesity can ultimately cause a disturbance in the metabolic crosstalk between multiple tissues such as the liver, skeletal muscle, and pancreas[4] leading to dyslipidemia, ectopic fat deposition, insulin resistance, and impaired glucose tolerance.[5–7] While dietary and lifestyle interventions aimed at weight loss have been shown to improve metabolic health in overweight and obesity[8–10] the large inter-individual variation in response to these interventions complicates both the assessment and provision of effective intervention options.

Currently, much of the evidence that underlies lifestyle intervention recommendations are obtained from large epidemiological or clinical studies. In nutritional research, the gold-standard for assessing intervention success is the randomized, double-blinded, placebo-controlled trial,[11,12] whereby the effectiveness of a given diet intervention is determined by comparing the change in an outcome measure such as body weight or fasting glucose in the intervention group to a control group.[13] By reducing the population level response to averages, or generic cut-offs, these studies often neglect the sometimes-considerable inter-individual variation that may exist in intervention effect. Indeed, the phenomenon of so-called responders and non-responders is frequently observed in nutritional intervention studies.[14,15] In recent years, the retrospective analysis of a number of dietary intervention studies separating participants into subgroups based on phenotypic features such as tissues specific insulin resistance,[16] glucose tolerance status,[17] or acetylcarnitine profile[18] have demonstrated that intervention success may be modulated by these underlying metabolic characteristics. More recently, a prospective, randomized, isocaloric dietary intervention trial reported diet specific improvements in metabolic health were mediated by tissue-specific insulin sensitivity status.[19] These findings coupled with advances in high-throughput omics technologies, allowing for deeper phenotyping of study participants, have given rise to the

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emergence of the field of personalized or precision nutrition. Whereby, nutritional advice is targeted toward the specific characteristics of an individual such as genotype, microbiome composition, or a specific metabolic trait to provide improved and more sustainable health outcomes for the individual.[20,21]

The potential for precision nutrition has been demonstrated by Zeevi et al., with their 2015 study revealing that phenotypic features such as gut microbiota composition could explain much of the observed inter-individual variation in the glucose excursions following a meal.[22] In a follow-up study, personalized dietary recommendations based on microbiota composition were shown to yield greater improvements in glycemic control than a Mediterranean diet.[23] While the success of these targeted diets demonstrates the potential advantages of moving away from population level nutritional advice and toward individual assessment, the diet prediction algorithm applied in these studies has been trained to reduce the 2-h postprandial glucose excursion alone, neglecting other crucial aspects of metabolic health. As the metabolic disturbances in overweight and obesity are not only characterised by deviations in glycemic control but also in disturbances in lipid metabolism, there is still a need for approaches to account for this multi-factorial definition of metabolic health when assessing intervention success.

While a number of simple indices to quantify features of metabolic health from fasting and meal response data have been proposed in the literature these indices primarily focus on the glucose-insulin system.[24–26] Moreover, as these indices typically rely on average metabolite levels or area under the response curve they fail to account for dynamic properties of the meal response curve such as peak height and time which may have clinical relevance.[27] The Mixed Meal Model is a physiology-based computational model that explicitly accounts for the insulin-mediated interactions between glucose, triglyceride, and non-esterified fatty acids (NEFAs).[28] Application of the Mixed Meal Model to population data has shown that the model captures features from meal responses that are indicative of glucose homeostasis such as insulin resistance and β-cell functionality but also properties related to lipid metabolism such as hepatic fat accumulation. In this way, the multi-variate time series of meal response data can be reduced to a low-dimensional interpretable set of parameters allowing for the assessment of intervention effects on multiple features of metabolic health at once. However, as of yet, the Mixed Meal Model has only been applied to average meal responses.

In this study we aim to assess the ability of the Mixed Meal Model to quantify metabolic resilience at the individual level by generating a population of personalized models using meal response data from three independent dietary intervention studies. The ability of the personalized Mixed Meal Model parameters to capture distinct components of metabolic health such as insulin resistance, β-cell functionality, and hepatic lipid accumulation will be verified by comparison to gold standard measures such as the hyperinsulinemic-euglycemic clamp and Magnetic Resonance Imaging measures of body composition. Moreover, by comparing personalized models generated before and after the dietary interventions we will show that the Mixed Meal Model can be used to assess the impact of the diet intervention on multiple aspects of metabolic health at the individual level, demonstrating the potential for personalized computational models in the application of precision nutrition in middle-aged individuals with overweight and obesity.

RESULTS

The Mixed Meal Model is a physiology-based mathematical model that describes the postprandial interplay between plasma glucose, insulin, triglycerides, and non-esterified fatty acids. The model consists of 13 coupled ordinary differential equations and 25 kinetic parameters that govern the release of endogenously produced glucose and triglyceride from the liver and NEFAs from the adipose tissue in the fasting state as well as the appearance of meal-derived glucose and triglyceride via the gut. The model also describes the secretion of insulin from the pancreas in response to elevated plasma glucose concentrations and insulin-stimulated uptake of glucose and triglyceride into the peripheral tissues. In previous work, the Mixed Meal Model has been shown to describe the average response to a mixed meal well. Moreover, by altering specific model parameters the Mixed Meal Model could simulate the effect of insulin resistance and elevated liver fat on the meal response. Here we set out to generate personalized models by fitting to individual meal response data. To generate a personalized Mixed Meal Model subject-specific characteristics such as body weight, fasting glucose and insulin, and the macronutrient composition of the ingested meal are supplied as input to the Mixed Meal Model. A set of eight personalized model parameters (Table 1) are then estimated by fitting the model to the meal response *in silico* by minimizing the sum of squared error between the model simulation and measured post-meal trajectories of plasma glucose, insulin, triglyceride, NEFAs (Figure 1). In this way, the dynamic features of the multi-variate time series of meal response data are reduced to an eight-dimensional health space. Personalized Mixed Meal Models were generated for subjects from the NutriTech,[29] MetFlex,[30] and BellyFat[31] studies by fitting the model to the measured mixed meal challenge test data.

Personalized Mixed Meal Models

A visual representation of personalized Mixed Meal Models for three individuals from the NutriTech Study is depicted in Figure 2. The personalized models were generated by fitting the model to measured plasma trajectories of glucose, insulin, triglyceride, and NEFA in response to a standardized high fat, high glucose mixed meal challenge test[32] performed before the diet intervention period. The personalized model simulations produce a good agreement with the measured meal response data. Moreover, these individuals demonstrate that the model is capable of capturing diverse meal responses with individual 33 (Figures 2B and 2C) having lower postprandial glucose and insulin excursions than individual 13 and a substantially lower triglyceride response than individual 13 (Figure 2E) to the same standardized meal. In addition, the Mixed Meal Model can infer rates of internal reactions which were not directly measured. In Figure 2D the model predicted rates of endogenous triglyceride release from the liver are visualized. Individual 37 is predicted to have a substantially higher rate of triglyceride secretion from the liver with the estimated value of k_{16}, the model parameter governing endogenous triglyceride secretion, being 0.022 mmol/L/min which is more than three times the rate estimated for individual 13 and five times greater than individual 33. This model

Table 1. List of estimated model parameters and their function in the Mixed Meal Model

Parameter Name	Function
k_1	Rate of glucose appearance from ingested meal
k_5	Rate of insulin dependent glucose uptake to peripheral tissues.
k_6	Rate of insulin secretion in response to increase in plasma glucose from basal value.
k_{11}	Rate of lipolysis of circulating triglycerides (LPL)
k_{12}	Rate of NEFA uptake into peripheral tissues.
k_{14}	Rate of appearance of triglyceride from ingested meal.(chylomicron)
k_{16}	Basal rate of endogenous triglyceride from the liver (VLDL)
τ_{LPL}	Time delay coefficient for insulin's effect of triglyceride and NEFA.

List of names and functions of the parameters that are estimated from meal response data to generate a personalized Mixed Meal Model. For a full list of model parameters including values of fixed parameters please see Table S2.

inferred high rate of triglyceride secretion from the liver is reflective of the measured intra-hepatocellular lipid to water ratio (IHCL)[33] which is considerably higher for individual 37 at 37.6 than for individuals 13 and 33 at 7.2 and 1.3 respectively. In addition, despite their comparatively high liver fat accumulation individual 37 has a BMI of just 25.6 kg/m^2, making them leaner than either individual 13 (BMI = 35.8 kg/m^2) or individual 22 (BMI = 29.3 kg/m^2). Ergo, quantification of meal response data using the Mixed Meal Model can provide more insight into an individual's metabolic health than commonly used measures such as body weight or BMI. To explore the extent to which personalized model parameters correlate with independent measures of metabolic health we performed Spearman correlation between the estimated parameters and measures of insulin sensitivity, β-cell functionality, and ectopic fat deposition (Table 2). k_{11}, a model inferred measure of triglyceride metabolism, not only produced a strong correlation with measures of insulin sensitivity ($\rho = 0.71$ with the Matsuda index[25] and $\rho = -0.62$ with HOMA-IR[24]) but also with MRS measures of hepatic lipid accumulation, with $\rho = -0.66$ with IHCL (Table 2). k_{11} produced only a weak

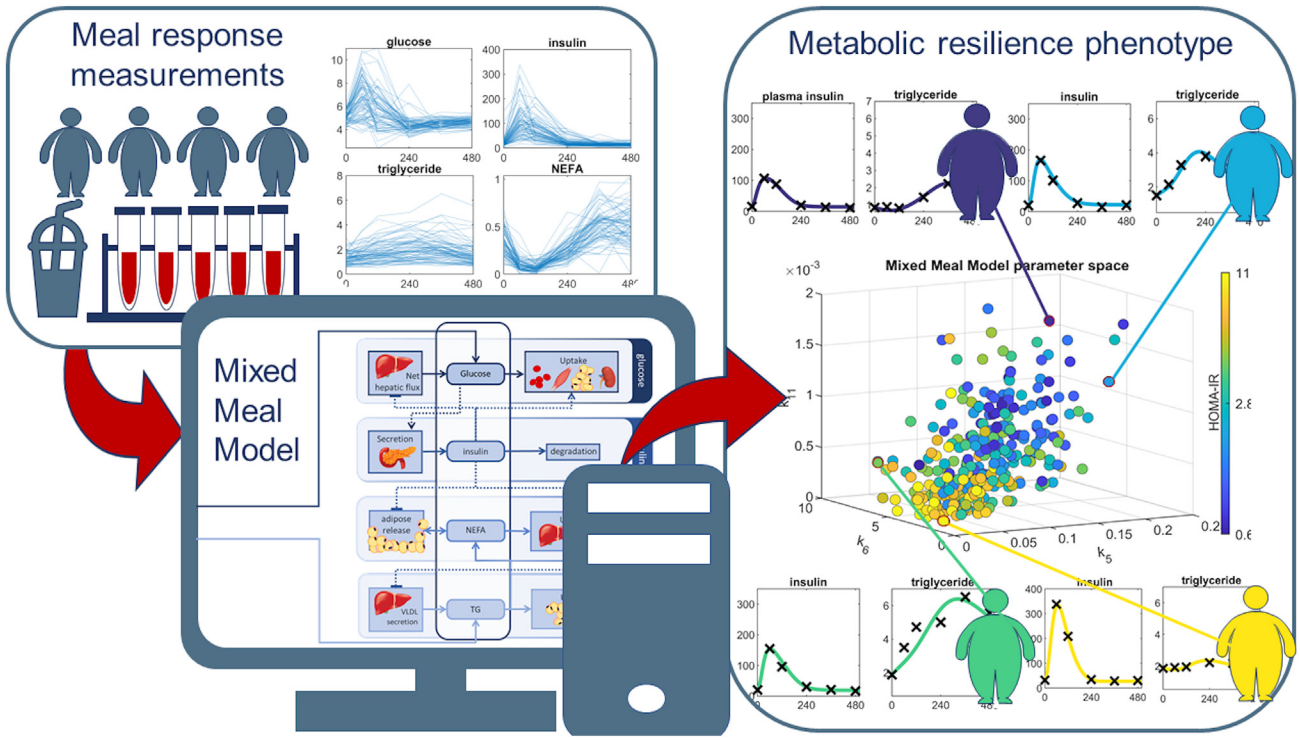


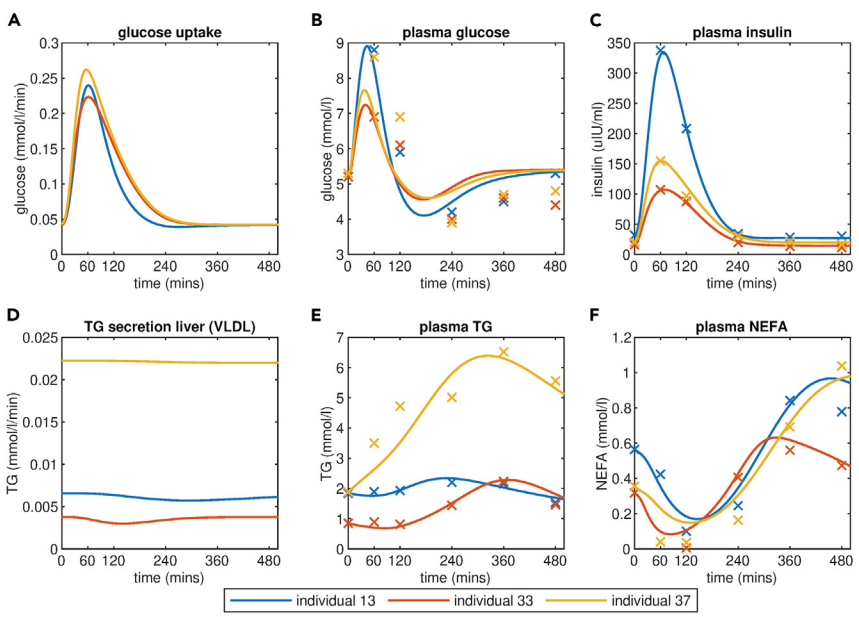
Figure 1. Scheme for generating personalized Mixed Meal Models to quantify metabolic resilience

A time series of the post-meal plasma trajectories of glucose(mmol/l), insulin(uIU/ml), triglyceride (mmol/L), and non-esterified fatty acids (mmol/L) are supplied as input to the Mixed Meal Model. Personalized parameter values are estimated by fitting the model to the measured time series data *in silico*. These parameter values infer features of metabolic resilience including insulin sensitivity, β-cell functionality, and liver lipid accumulation from the dynamic shape of the meal response curves of all four metabolites, thereby quantifying an individual's metabolic resilience.

Table 2. Spearman correlation coefficient between model parameters and independent measure of metabolic health

		NutriTech (n = 52)									MetFlex (n = 34)			
		Insulin sensitivity		B-cell function	Fat accumulation					BMI	Insulin sensitivity		Glycemic control	BMI
	parameters	Matsuda	HOMA-IR	IGI	liver	Muscle (tibialis)	Muscle (soleus)	pancreas	ASAT	BMI	M-value	HOMA-IR	HbA1c	BMI
k_5	Insulin sensitivity	**0.79**	**−0.73**	−0.43	**−0.65**	0.19	0.11	0.01	0.13	−0.31	**0.67**	**−0.39**	0.02	−0.24
k_6	Insulin secretion	−0.07	−0.12	**0.51**	0.03	−0.31	−0.13	−0.17	0.04	0.07	−0.24	0.06	−0.06	0.26
k_{11}	Triglyceride metabolism	**0.71**	**−0.62**	−0.25	**−0.66**	0.08	0.29	−0.05	−0.05	−0.21	**0.73**	**−0.50**	−0.33	−0.34

Table of Spearman correlation coefficients between personalized Mixed Meal Model estimates of k_5, a model derived measure of insulin sensitivity, k_6, an indicator of insulin secretion, and k_{11}, a marker of triglyceride metabolism, and independent measures of metabolic health for baseline data from the NutriTech (n = 52) and the MetFlex (n = 34) studies. Correlation coefficients with a p value<0.05 are indicated in bold. ASAT stands for the abdominal subcutaneous adipose tissue volume. A complete set of correlation coefficients between all Mixed Meal Model parameters and these independent measures of health can be found in Table S1.



parameters		Individual 13	Individual 33	Individual 37
k_5	Insulin sensitivity	0.012	0.042	0.034
k_6	Insulin secretion	3.522	1.800	2.503
k_{11}	LPL lipolysis	$1.6x10^{-4}$	$5.8x10^{-4}$	$2.1x10^{-4}$
k_{12}	NEFA uptake	0.020	0.043	0.033
k_{16}	TG secretion	0.007	0.004	0.022
Phenotypic information				
Insulin sensitivity	Matsuda	18.1	46.7	37.5
	HOMA-IR	6.4	2.9	4.1
B-cell function	IGI	37.0	30.1	28.7
	HOMA-β	286.4	193.1	204.6
Liver fat	IHCL	7.2	1.3	37.6
	BMI	35.8	29.3	25.6

Figure 2. Example of personalized Mixed Meal Model for three individuals from the NutriTech Study

Visualization of the model fit to the meal response of plasma (B) glucose, (C) insulin, (E) triglyceride, and (F) NEFA for three individuals from the NutriTech Study. Measured meal response data for each individual is indicated with the crosses, the personalized model simulation is depicted with a solid line. Model inferred rates of (A) glucose uptake into the tissues and (D) the triglyceride secretion by the liver are also visualized. Personalized parameter estimates as well as independent measures of metabolic health, including metrics of insulin sensitivity (Matsuda and HOMA-IR) and β-cell functionality (insulinogenic index (IGI) and HOMA-β) calculated using an oral glucose tolerance test and intrahepatocellular lipid to water ratio measured using magnetic resonance spectroscopy, for these three individuals are provided in the table to the right.

correlation with other measures of adiposity including BMI, abdominal subcutaneous adipose tissues and fat accumulation in skeletal muscle and pancreas. Estimated values for k_5, the model parameter describing the rate of insulin-dependent glucose uptake into the tissues, also produced a strong Spearman correlation with independent measures of insulin sensitivity with $\rho = 0.79$ with the Matsuda index (insulin sensitivity) and $\rho = -0.73$ for HOMA-IR (insulin resistance)(Table 2). Moreover, in the MetFlex study personalized estimates of k_5 has a Spearman correlation of $\rho = 0.67$ with the M-value of the hyperinsulinemic-euglycemic clamp, the gold standard measure for peripheral insulin sensitivity.[34] In addition, k_6, the parameter that governs insulin production, did not produce any significant correlation with independent measures of insulin sensitivity or liver fat but did produce a medium-strength significant correlation with the insulinogenic index, a surrogate index of β-cell functionality.[35,36] In this way, the personalized Mixed Meal Model parameters provide an integrated assessment of metabolic resilience from meal response data.

A depiction of Mixed Meal Model fits to meal responses and personalized parameter estimates for individuals from the MetFlex and BellyFat studies can be found in Figures S1 and S2. Applying the Mixed Meal Model to individual meal challenge test data collected both before and after the diet intervention periods across all three studies resulted in 342 personalized models.

Mixed Meal Model as a definition of metabolic resilience

To further evaluate the Mixed Meal Model parameter space as a definition of metabolic resilience principal component analysis was performed on the parameter values from 342 personalized models. No distinct clusters of individuals were found (Figures 3 and S3). The first three principal components capture 66.4% of the variance in the personalized parameter estimates. The loading vectors for the PCA demonstrate that parameters grouped by the function ascribed to them within the Mixed Meal Model, k_{11}, k_{12}, and k_{16} govern lipid metabolism, k_5 is the model derived measure of insulin sensitivity, k_6 defines insulin secretion, and k_1 and k_{14} describe the appearance of glucose and triglyceride from the meal respectively. Coloring the PCA scores by HOMA-IR, an independent measure of insulin resistance, shows that there is a clear trend in the Mixed Meal Model parameter space (Figure 3A) with insulin sensitivity decreasing along the directions of loading vectors for k_5 (insulin sensitivity) and the lipid parameters k_{11}, k_{12}, and k_{16}.

Scatterplots provide a visual representation of the correlations between the three parameters that capture the key features of metabolic resilience, namely insulin sensitivity (k_5), β-cell capacity (k_6), and liver fat accumulation (k_{11}) and independent measures of metabolic health. In Figure 3B visualizes all 342 individuals, demonstrating that insulin resistance as measured with HOMA-IR decreases as the model-derived measure of insulin sensitivity (k_5) increases. Figure 3C looks at the same relation for the subset of individuals from the NutriTech Study colored by the insulinogenic index, a measure of β-cell functionality. In this instance increases in the value of the insulinogenic index coincide with increases in the value for k_6, the model parameter attributed to insulin secretion, along the y axis. Finally, Figure 3D shows that greater hepatic

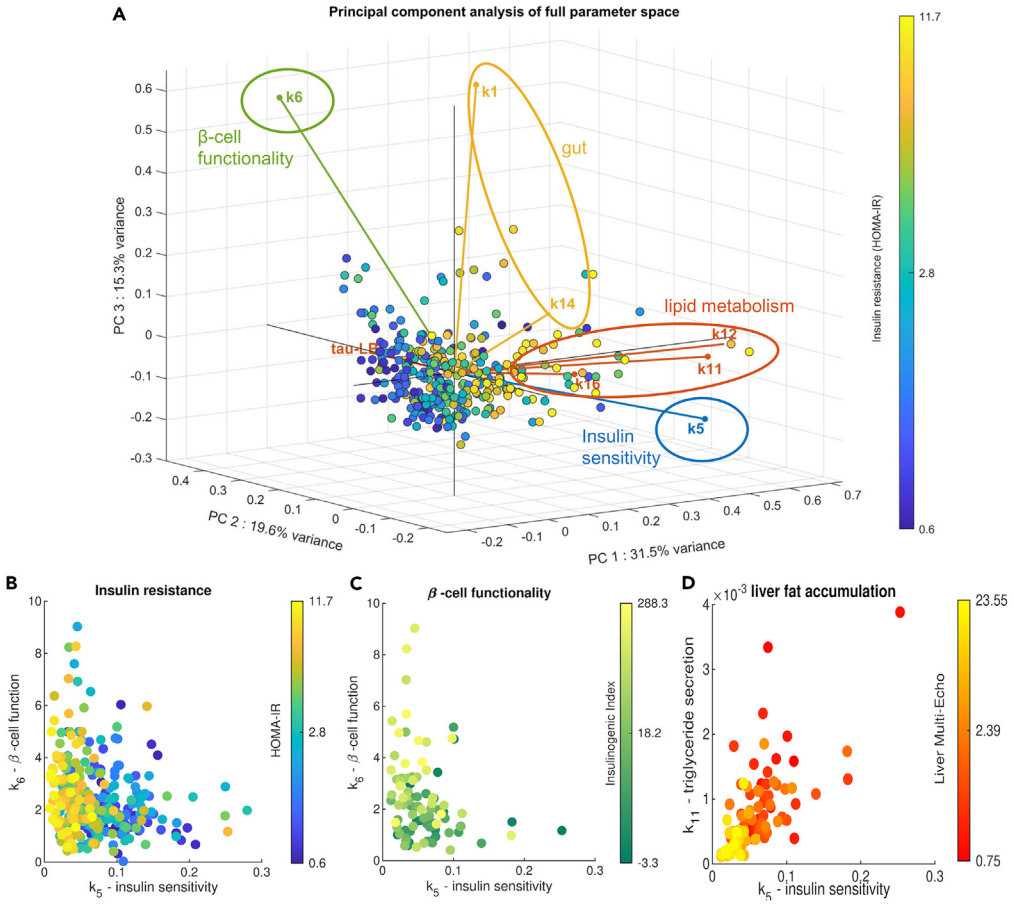


Figure 3. Mixed Meal Model parameter space as a definition of metabolic resilience

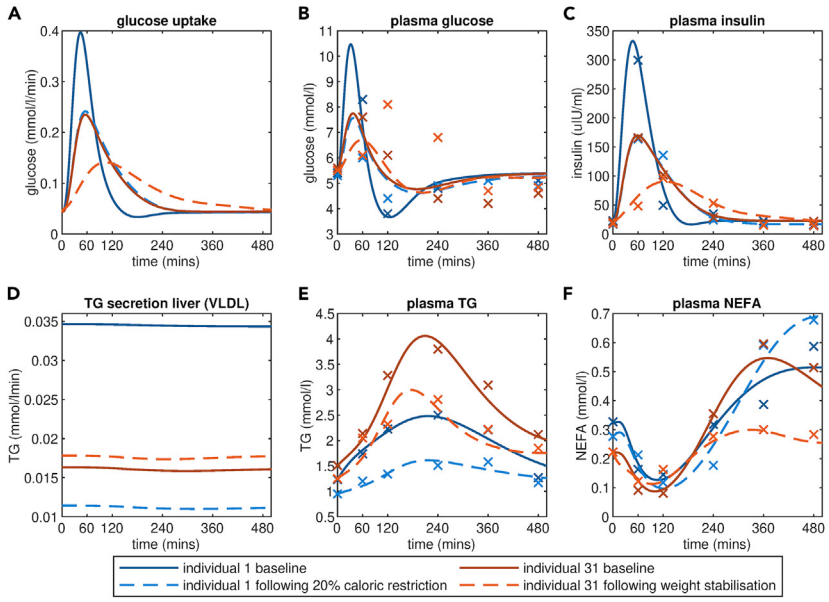
Evaluation of personalized Mixed Meal Model parameter values as a metric of metabolic resilience.

(A) Principal component analysis of the 8-dimensional parameter space generated from 342 personalized Mixed Meal Models. The projection of study participants along the first three principal components is visualized. Each data point (subject) is colored by their HOMA-IR value, an independent measure of insulin resistance. The model parameter loadings are also visualized and colored by the parameter's role in the Mixed Meal Model; k_1 and k_{14} govern the rate of appearance of glucose and triglyceride from the gut(yellow), k_5 is the parameter ascribed to insulin sensitivity (blue), k_6 the parameter attributed to β-cell functionality (green), and k_{11}, k_{12}, k_{16}, and τ_{LPL} are the parameters governing lipid metabolism (red). In (B) a scatterplot of the personalized values of k_5 and k_6 colored by HOMA-IR (independent measure of insulin resistance) show that an increase in the value for k_5 (the Mixed Meal Model derived metric of insulin sensitivity) corresponded with a decrease in measured insulin resistance. In (C) the same scatterplot is colored by the insulinogenic index (an independent measure of β-cell functionality) for the individuals from the NutriTech Study. Here on the y axis as the value of k_6 increases so too does the value for the insulinogenic index as indicated by the lighter shade of green. In (D) a scatterplot of the personalized values of k_5 and k_{11} colored by liver fat as measured with MRS data show that lower values for both k_5 and k_{11} correspond with higher measures of liver fat (yellow color). A complete set of scatterplots visualizing the relationship between k_5, k_6, and k_{11} colored by several independent measures of metabolic health can be found in Figures S3 and S4.

lipid accumulation coincides with lower values of both insulin sensitivity (k_5) and triglyceride metabolism (k_{11}). This demonstrates that the personalized Mixed Meal Model captures and quantifies metabolically relevant indicators of health from meal challenge test data. Visual comparison of personal estimates for k_5, k_6, and k_{11} and a complete range of independent measures of metabolic health can be found in Figures S4–S6.

Personalized assessment of nutritional interventions

Personalized Mixed Meal Models were from the meal responses for each individual both before and after the different dietary interventions. No significant differences in metabolic resilience defined by Mixed Meal Model parameters was observed when comparing the mean change in parameter values for the diet intervention groups to the control groups from the NutriTech, MetFlex, or BellyFat Studies using a Kolmogorov-Smirnov test. In fact, there was no consensus in the direction of change of the personalized parameter estimates in either the control or intervention groups, demonstrating the oversight that may occur when evaluating intervention effects at the group level (Figures S7–S9). Figure 4 visualized the personalized Mixed Meal Models generated before and after the 12 weeks intervention period for



parameters		20% caloric restriction		Weight stabilisation	
		Individual 1		Individual 31	
		baseline	Follow-up	baseline	Follow-up
k_5	Insulin sensitivity	0.020	0.027	0.026	0.033
k_6	Insulin secretion	3.160	3.201	3.175	0.977
k_{11}	LPL lipolysis	6.8×10^{-4}	4.9×10^{-4}	2.3×10^{-4}	3.7×10^{-4}
k_{12}	NEFA uptake	0.061	0.033	0.044	0.061
k_{16}	TG secretion	0.035	0.011	0.016	0.018
Phenotypic information					
Insulin sensitivity	Matsuda	25.1	32.2	31.3	43.4
	HOMA-IR	4.5	3.4	4.4	4.5
B-cell function	IGI	22.3	19.5	21.9	9.8
	HOMA-β	209.5	163.2	234.0	185.6
Liver fat	IHCL	13.7	5.5	15.3	20.4
	BMI	26.7	24.6	29.3	28.7

Figure 4. Application of Mixed Meal Model to assess the impact of a 12-week dietary intervention on metabolic resilience

Visualization of personalized Mixed Meal Models generated for two individuals from the NutriTech Study. Individual 1 underwent a 12-week period of 20% caloric restriction (blue) and individual 31 undertook a weight maintenance diet for a 12-week period (red). A model is generated for each individual using the baseline data (solid line) and a second model is generated using data collected following the 12-week intervention period (dashed line) to assess the impact of the intervention on each subject's metabolic resilience. The model simulated postprandial trajectories of plasma (B) glucose, (C) insulin, (E) triglyceride, and (F) NEFA are shown along with the measured meal response data used to generate the personalize models. The Mixed Meal Model also allows for the inference of the postprandial (A) net hepatic glucose flux and (D) rate of triglyceride secretion from the liver. Personalized model parameter estimates and independent measured of metabolic health, including metrics of insulin sensitivity (Matsuda and HOMA-IR) and β-cell functionality (IGI and HOMA-β) calculated using an oral glucose tolerance test and intrahepatocellular lipid to water ratio measured using magnetic resonance spectroscopy, collected before and after the intervention period are provided on the right.

a subject who undertook a weight stabilization diet and a subject who had a 20% caloric restriction intervention from the NutriTech study. Here the impact of the intervention can be assessed at the individual level. For both subjects the model predicts a small improvement in insulin sensitivity, which is supported by an increase in their respective Matsuda values calculated from their OGTT data. The Mixed Meal Model predicts a small increase in liver fat for the subject on the weight stabilization diet (Figure 4D), with increases in k_{11} (2.3×10^{-4} mmol/L/min at base line to 3.7×10^{-4} mmol/L/min following the intervention) and k_{16} (0.016 mmol/L/min at baseline to 0.018 mmol/L/min following intervention) parameters defining triglyceride metabolism. For the individual who underwent the 20% caloric restriction diet the Mixed Meal Model indicated a substantial decrease in liver fat, with k_{16} reducing from 0.035 mmol/L/min to 0.011 mmol/L/min corresponding with a decrease in IHCL from 13.7 to 5.5 measured using MRS. Application of the Mixed Meal Model to investigate the impact of the diet intervention applied in the MetFlex and Bellyfat studies can be found in Figures S10 and S11.

DISCUSSION

The multifaceted nature of the metabolic deteriorations associated with overweight and obesity such as dyslipidemia, insulin resistance, and hyperglycemia complicate the evaluation of nutritional and lifestyle interventions as not only is the population highly heterogeneous but also the potential benefits of an intervention need to be assessed across multiple factors.[8,10] In this study we demonstrated the ability of personalized *in silico* models of metabolism to provide a holistic measure of metabolic health in people with overweight and obesity, providing a comprehensive assessment of intervention effects on metabolic health at the individual level. By quantifying the sources and drivers of the observed inter-individual variation in metabolic resilience in people with overweight and obesity the Mixed Meal Model forms an essential step in the transition toward precision nutrition.

Multiple surrogate indices for insulin resistance or β-cell functionality have already been proposed in the literature.[37] Simple measures such as HOMA-IR, Matsuda, or the insulinogenic index are frequently employed in nutritional research as an alternative to more invasive and costly gold standard measures such as the hyperinsulinemic-euglycemic clamp. The Mixed Meal Model provides an alternative to these indices; quantifying not only insulin sensitivity but also β-cell functionality and liver fat accumulation. Moreover, several of these existing metrics, such as the muscle insulin sensitivity index or hepatic insulin resistance index, have only been validated for application to oral glucose tolerance test data and cannot be readily extrapolated to mixed meal responses.[26,38,39] Combining data from the NutriTech, MetFlex, and BellyFat studies included in these analyses a population of 342 personalized Mixed Meal Models could be generated. Coloring the PCA of the

resulting Mixed Meal Model parameter space by the study origin (Figure S3) demonstrated that there was no effect of the study on the estimated parameter values, indicating that personalized Mixed Meal Model parameters are invariant to the macro-nutrient composition of the meal, sampling schedule of the challenge test, center, and study population. The macro-nutrient composition of the meal along with body weight in kg are supplied as input to the model during the personalization procedure. In this way the effects of meal composition or substantial differences in body weight that might impact the measured plasma metabolite concentrations are corrected for, meaning that the parameters are capturing changes in metabolic fluxes. We postulate that the Mixed Meal Model provides a superior metric of metabolic health than existing indices as it quantifies deteriorations in both lipid and glucose metabolism and is invariant to meal composition.

The Mixed Meal Model was readily personalizable, with the model producing a satisfactory fit to diverse meal responses measured in individuals with overweight and obesity from three independent study populations included in these analyses. Moreover, we showed the personalized parameter estimates also capture physiologically relevant markers of metabolic health from the dynamics of the postprandial plasma excursions of glucose, insulin, triglyceride, and NEFA; with the model-derived measure of insulin sensitivity (k_5) producing a strong correlation with independent measures of insulin resistance including the hyperinsulinemic-euglycemic clamp, the gold standard measure of peripheral insulin sensitivity[34] (Table 2). The Mixed Meal Model also moves beyond current glucocentric indices of metabolic health with the model inferred rates of triglyceride metabolism (k_{11}) producing a strong correlation ($\rho = -0.66$) with independent measures of hepatic lipid accumulation (Table 2). This is stronger than the correlation found between IHCL and both the triglyceride-glucose (TyG) index ($\rho = 0.57$), a predictor of NAFLD,[40,41] and the lipid accumulation product ($\rho = 0.59$), a surrogate measure of hepatic fat accumulation proposed by Khan.[42] Moreover, we see this correlation between model parameters of lipid metabolism is specific for fat accumulation in the liver with no significant correlations found between k_{11} and measures of fat accumulation in the skeletal muscle, pancreas, or the volume of abdominal subcutaneous adipose tissue (Figure S6).

Comparison of parameter estimates from before and after diet interventions did not reveal any statistically significant changes when compared to the control groups. Analysis of the NutriTech study population by Rundle at al. reported a statistically significant reduction in HOMA-IR values following 12 weeks at 20% energy restriction.[29] While we do see an increase the mode for distribution of k_5, the model-derived measure of insulin sensitivity, in the 20% energy restriction group in the NutriTech study indicating a general improvement in insulin sensitivity, It is not significantly different from the what we see in the control group. The individual trends elucidate the large inter-individual variation in intervention response with parameter estimates increasing for some individual and decreasing for others in both the intervention and control groups (Figures S7–S9). In this study, we have demonstrated the ability of the Mixed Meal Model to quantify the effect of a dietary intervention on the metabolic health of an individual. In Figure 4, personalized parameter estimated for individual 1 indicated there was a substantial decrease in the rate of endogenous triglyceride secretion from the liver following 12 weeks of 20% calorie restriction, which was validated with MRS measures of hepatic lipid accumulation. Moreover, as the Mixed Meal Model quantifies metabolic health it can provide a more relevant assessment of intervention success in metabolically impaired individuals such as those with overweight and obesity than reductions in body-weight or BMI alone.

Post-hoc analysis of multiple dietary intervention studies have demonstrated that tailoring diets toward specific metabolic deteriorations such as tissues specific insulin resistance can yield better results for study participants.[16–18,22] We evaluated the Mixed Meal Model parameter space as a predictor of intervention success. However, the various diet groups available in this study contained at most thirty-five individuals which made the formation of subgroups to effectively train and test such a prediction model prohibitive. In future work the application of the Mixed Meal Model to larger groups could allow for the evaluation of the metabolic health profile defined by personalized parameter estimated as a predictor of response to diet. In this way the Mixed Meal Model can facilitate the transition toward precision nutrition, by quantifying specific metabolic deviations that can be improved by targeted nutritional or lifestyle interventions, achieving a better and more sustainable outcome for the individual.

The Mixed Meal Model failed to fit the meal response data of approximately 12% of the study population (Figure S12). Sparse sampling of the early phase of the meal response in the NutriTech Study with measurements at 0, 60, and 120 min meant that in some instances the faster dynamics of glucose and insulin were missed, in these instances model fitting often failed. In future studies we recommend more frequent sampling of glucose and insulin during the first hour of meal responses to ensure the faster meal dynamics are captured, reducing this source of model failure. The studies included in this analysis also varied in their sampling duration, with MetFlex sampling up to 300 min and NutriTech sampling up to 480 min after the meal. A sensitivity analysis of sampling duration indicated there was a large difference in the estimates of parameters governing lipid metabolism (k_{11}, k_{12}, k_{14}, k_{16}, and τ_{LPL}) when comparing data from 240 min with data collected over 360 min and 480 min (Figure S13; Table S3). Based on these results we would also recommend collecting blood samples for at least 300 min following consumption of the meal. We have shown the Mixed Meal Model is sufficiently generalizable to fit the meal response data from three independent dietary intervention studies. However, all three study populations consisted of middle-aged men and women of European decent with overweight and obesity. In the future it would be necessary to evaluate the performance of the Mixed Meal Model on more diverse populations including lean individuals, people with Type 2 Diabetes Mellitus, and individuals with diverse ethnic backgrounds before the model could be recommended for widespread use. Moreover, in this study personalized models were generated independently for each subject, neglecting the fact that the individuals in each study had to meet specific inclusion and exclusion criteria and therefore come from a comparatively homogeneous study population. In future work, use of mixed-effects parameter estimation strategies that take this population structure into account could better constrain parameter estimates to population distribution thereby allowing for better inference personalized models given sparse or missing data.[43] In addition, the Mixed Meal Model is a homeostatic model.[44] Without external perturbation in the form of a meal plasma concentrations of glucose and insulin will remain stationary at the specified basal values. The measured fasting glucose

concentration is supplied as the basal glucose value to the model,[45,46] consequently the model struggles when the plasma glucose concentration falls below the basal values. In instances where the second glucose measurement is lower than the initial fasting value the Mixed Meal Model fitting often fails (Figure S14). Modification of the Mixed Meal Model equations to remove this dependency on the basal values in the future could reduce this source of model failure.

Here, we assume a single meal response is sufficient to capture metabolic resilience. While the personalized parameter estimates produce a strong correlation with independent measures of health suggesting they are indeed capturing physiologically relevant features of metabolic resilience, the reproducibility of the meal response itself needs to be confirmed. A number of previous studies have demonstrated that there can be substantial intra-individual variation in the response to an oral glucose tolerance test.[47–49] A study where subjects undergo repeated meal challenge tests without an intervention in between is necessary to quantify the intra-individual variation in Mixed Meal Model parameters and to better establish the level of uncertainty that accompanies personalized parameter estimates. Moreover, to observe the post-meal trajectories of plasma metabolites meal challenge tests require multiple blood samples to be drawn, this is not only invasive and burdensome for the participant but limits the applicability of challenge tests outside of the research setting. In recent years there have been considerable advances in the development of wearable technologies for continuous glucose monitoring,[50] meaning that it is now possible to generate extensive time series of interstitial glucose excursions in response to daily activities. By coupling continuous glucose measurements with dried blood spot measurements of triglyceride and c-peptide, a marker of insulin secretion, as has been done in the Predict study[51] personalized Mixed Meal Models could be generated without the need for invasive sampling techniques. In this way the Mixed Meal Model could go beyond the assessment of intervention success in clinical trials and be combined with continuous data collected through wearable devices to give real time feedback to people with overweight and obesity forming a Digital Metabolic Twin.[52] Such a Digital Metabolic Twin could be used to quantifying how dietary and lifestyle choices are impacting an individual's metabolic health and relay this information back to the user.

Currently the Mixed Meal Model is implemented in MATLAB which may prohibit its use by researchers with limited programming experience. To circumvent this challenge, we also developed the Mixed Meal Calculator, a stand-alone application with a user-friendly graphical interface that allows users to enter their own meal challenge test data, specifying subject specific characteristics such as body-weight and meal composition to generate a personalized Mixed Meal Model. The Mixed Meal Model Calculator can be found in Folder S2 or downloaded from https://github.com/shauna-odonovan.

In conclusion, the Mixed Meal Model provides a holistic measure of health, quantifying insulin resistance, β-cell functionality, and liver fat accumulation from the plasma trajectories of glucose, insulin, triglyceride, and NEFA following a meal. By simultaneously capturing and quantifying multiple aspects of metabolic health the Mixed Meal Model not only allows us to get a grip on the considerable inter-individual variation observed in people with overweight and obesity but also allows for the evaluation of intervention effects on specific components of metabolic health at an individual level. Moreover, personalized Mixed Meal Models can facilitate the transition toward precision nutrition by revealing disturbances in specific metabolic sub-systems that can be targeted by tailored dietary interventions.

Limitations of the study

While we have applied the Mixed Meal Model to meal response data from three independent dietary intervention studies, all three study populations consisted of middle-aged men and women of European decent with overweight and obesity. In the future, the Mixed Meal Model should be further validated on more diverse populations including lean individuals, people with Type 2 diabetes mellitus, and individuals with diverse ethnic backgrounds before the model could be recommended for widespread use. In addition, the Mixed Meal Model failed to fit the meal response data of approximately 12% of the study populations included in this analysis. These failures could be in part attributed to sparse sampling of the early phase of the meal response which fails to capture the more rapid glucose and insulin dynamics in the first 2 h after the meal. Furthermore, the Mixed Meal Model is currently formulated as a homeostatic model, with the measured fasting glucose concentration supplied to the models as the basal glucose value, as a result the model struggles when the plasma glucose concentration falls below the basal values. In the future, modification of the Mixed Meal Model equations to remove this dependency on the basal values could reduce this source of model failure.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- METHOD DETAILS
  - Data
  - The mixed meal model
- QUANTIFICATION AND STATISTICAL ANALYSIS
- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109362.

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AUTHOR CONTRIBUTIONS

Conceptualization, L.A.A., I.C.W.A., S.D.O'D., and N.A.W.v.R.; Methodology, S.D.O'D. and N.A.W.v.R.; Resources, L.A.A., M.v.B., J.D.B., G.F., A.K.G., D.M.J., E.C.M.M., M.N., M.R., L.S., E.L.T., and A.J.W.; Software, S.D.O'D.; Formal Analysis, S.D.O'D.; Writing – Original Draft, S.D.O'D; Writing – Review & Editing, L.A.A, I.C.W.A, M.v.B., J.D.B., G.F., A.K.G., D.M.J., E.C.M.M., M.N., S.D.O'D., M.R., L.S., E.L.T., N.A.W.v.R., R.d.V., and A.J.W.; Funding Acquisition, L.A.A., I.C.W.A., and N.A.W.v.R.; Supervision, L.A.A., I.C.W.A., and N.A.W.v.R.

DECLARATION OF INTERESTS

D.M.J. and A.J.W. are employees of Unilever, which manufactures and markets consumer food products. L.S. is CEO and M.N. is in the scientific board of Caelus Pharmaceuticals, the Netherlands. However, these positions are not directly relevant for the content of this current paper. S.D.O'D., M.R., E.L.T., J.D.B., G.F., R.d.V., E.C.M.M., M.v.B., L.S., M.N., A.K.G., I.C.W.A., N.A.W.v.R., and L.A.A. declare no conflicts of interest.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
NutriTech Study meal responses	Rundle et al.[29] (2023) https://doi.org/10.1016/j.ajcnut.2023.07.002	Nutritional Phenotypes Database https://studies.dbnp.org/NutriTechHIS
MetFlex Study meal responses	Fechner et al.[30] (2020) https://doi.org/10.1016/j.clnu.2019.12.010	https://hive.unilever.com/
BellyFat Study meal responses	Schutte et al.[31] (2022) https://doi.org/10.1093/ajcn/nqac025	https://research.wur.nl/en/projects/belly-fat
Software and algorithms		
MATLAB 2019b	The MathWorks Inc.	RRID: SCR_001622
Other		
Original Mixed Meal Model code	This paper	https://github.com/shauna-odonovan

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Shauna O'Donovan (s.d.odonovan@tue.nl).

Materials availability

This study did not generate any new unique reagents.

Data and code availability

- The NutriTech, MetFlex, and BellyFat meal challenge test data used in this study are unsuitable for public deposition due to ethical restrictions and privacy of participant data. NutriTech data is available to qualified researchers via the Nutritional Phenotypes Database (https://studies.dbnp.org/NutriTechHIS) or by contacting Lydia A. Afman (lydia.afman@wur.nl). The MetFlex data is available from Unilever for any interested research who meets the criteria to access confidential data please contact Doris M. Jacobs (Doris.Jacobs@unilever.com) or Anne J. The BellyFat data is available from the Division of Human Nutrition and Health, Wageningen University for any interested researcher who meets the criteria for access to confidential data, please contact Lydia A. Afman (lydia.afman@wur.nl).
- All original code is provided in the supplementary materials and has also been deposited in GitHub (https://github.com/shauna-odonovan).
- Any additional information required to re-analyse the data reported in this paper is available from the lead contact upon request.

METHOD DETAILS

Data

NutriTech study

The NutriTech Study is a dietary intervention study funded as part of the European Union 7th Framework Program which aimed to better phenotype human volunteers in response to standardized challenge tests.[29] As part of this study 72 overweight and obese (BMI 24.9–35.8 kg/m^2) men and women (48.6% male) aged between 50 and 65 years were randomized to undertake either a supervised diet with a 20% reduction in caloric restriction or a weight maintenance diet for a period of 12 weeks.[18] Both before and after the intervention period all subjects were comprehensively phenotyped including MRI scanning to assess body composition and a series of challenge tests to characterize metabolic resilience. Challenge tests began at 9a.m. following a 12-h over-night fast. On day one subjects underwent a standard 75 g oral glucose tolerance test (OGTT) were blood samples were collected at 0, 15, 30, 60, 90, 120, and 240 min following intake of the glucose bolus. On day two the study participants partook in a high-fat, high-glucose liquid meal challenge test (75 g glucose, 60 g lipid (palm olein), and 20g Protifar as milk protein concentrate (Nutricia, Utrect, the Netherlands)[32]). The liquid meal was consumed within 5 min, and blood was collected at 0, 60, 120, 240, 260, and 480 min following ingestion of the shake. Plasma concentrations of glucose, insulin, triglycerides, and non-esterified fatty acids (NEFA) were measured in all samples. Due to incomplete meal challenge test data three individuals were removed from the NutriTech Study dataset for our analysis, resulting in a dataset of 69 individuals. OGTT measures of glucose and insulin are used to calculate several metrics of metabolic health including HOMA-IR[24] and the Matsuda Index,[25] measures of whole-body insulin resistance, and

HOMA-β and the Insulinogenic Index,[35,36] surrogate measures of β-cell functionality. In addition, each subject's body composition, including liver fat content, were assessed with MRI and spectroscopy on a 1.5 T multinuclear system (Philips, Eindhoven, the Netherlands) as previously described.[33] All subjects gave written and informed consent before participating in the NutriTech Study. The NutriTech Study was performed according to the guidelines stated in the Declaration of Helsinki and received ethical approval from the Brent Ethics Committee (REC ref. 12/LO/0139) and was registered at www.clincaltrials.gov as NCT01684917.

MetFlex study

The MetFlex study is a dietary intervention study in which 40 overweight and obese (BMI 25-35 kg/m^2) men and women (47.5% male) were randomly assigned to one of two isocaloric diet groups for a period of six weeks; either a low-quality diet (western diet) or a high-quality diet (low in high-glycaemic carbohydrates and rich in fruits, vegetables, fibers, and polyunsaturated fats[30]). Both before and following the diet intervention period all study participants underwent a liquid mixed meal challenge test (67 g carbohydrate, 36 g lipids, and 12 g protein) following an over-night fast. Following consumption of the meal blood samples were collected at 0, 15, 30, 45, 60, 90, 120, 180, 240, and 300 min. Plasma glucose and insulin concentrations were determined at all time points. Plasma triglyceride and NEFA levels were measured at 0, 30, 60, 120, 180, 240, and 300 min. In addition, both before and after the intervention all subjects underwent a 2.5 h 1-step hyperinsulinemic-euglycemic clamp with an insulin infusion rate of 40 mU/m^2/min to quantify peripheral insulin sensitivity.[34] All study participants gave their written and informed consent prior to the commencement of the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the medical ethical committee of the Maastricht University Medical Center+ (MUMC+) and was registered at www.clincaltrials.gov as NCT02519127.

BellyFat study

The BellyFat Study is a dietary intervention study which aimed to study the effects of nutrient quality as well as energy restriction on weight-loss. As part of this study 110 overweight and obese (BMI 25.5–41.7 kg/m^2) men and women (46%) male aged 40–70 years were randomised onto one of three diet arms; a 25% energy-restricted diet with high nutrient quality, a 25% energy restricted diet with low nutrient quality, or their habitual diet (control group) for 12 weeks.[31] As with the previous studies, both before and after the intervention period following an overnight fast all study participants underwent a high-fat, high-glucose mixed meal challenge test consisting of 76.3 g of carbohydrates, 60 g of fat, and 17.6 g of protein. Blood samples were collected at 0, 30, 60, 120, 180, 240, and 360 min. Plasma glucose concentrations were determined at all time points for the first 4 h of the meal, plasma insulin was measured at 0, 60, 120, and 240 min. Given the longer meal response times of lipid species plasma concentrations of both triglyceride and NEFA were measured at 0, 120, 240, and 300 min. Ten individuals did not complete the intervention and were removed from our analysis, resulting in a dataset consisting of 100 individuals (34 individuals in 25% ER + high-quality diet group, 39 individuals in the 25% ER + low-quality diet group, and 27 individuals in the control group). All subjects gave written and informed consent before participating in the BellyFat study. The study was conducted in accordance with the guidelines laid out in the Declaration of Helsinki. The BellyFat Study was approved by the Medical Ethics Committee of Wageningen University and registered at www.clinicaltrials.gov as NCT02194504.

The mixed meal model

The Mixed Meal Model is a physiology-based computational model describing the systemic insulin mediated interplay between glucose and lipid species.[28] The model consists of a system of thirteen coupled ordinary differential equations accounting for the key reactions governing the postprandial changes in plasma glucose, insulin, triglyceride, and NEFA concentrations. The Mixed Meal Model describes the rate of appearance of meal derived glucose and triglyceride in the plasma via the gut and lymphatic system respectively. The model also contains terms that explicitly account for the inhibition in the secretion of endogenous glucose and triglyceride from the liver as well as a reduction in the release of NEFA from the adipose tissues as a result of increases in insulin production in response elevated plasma glucose concentrations following the intake of a meal. Terms describing the lipolysis of circulating triglyceride as well as the uptake of glucose and NEFA into the tissues are also included in the model. The rate of metabolic fluxes through the reactions described in the Mixed Meal Model equations are governed by 21 kinetic parameters and 4 model constants. A complete list of model equations can be found in File S1.

QUANTIFICATION AND STATISTICAL ANALYSIS

In previous work, we have shown that the Mixed Meal Model could be reliably fit to population level meal response data by estimating a subset of nine model parameters from the data.[28] Here, we set about generating personalized Mixed Meal Models. To this end, the model individualisation pipeline proposed by Erdos et al. was implemented using the baseline meal response data from the NutriTech Study.[53] This analysis resulted in the identification of an eight-parameter model which produced the most parsimonious fit to the individual data (Table 1). The biological functions ascribed to the estimated model parameters as well as the value to which the remaining parameters are fixed are outlined in Table S2.

Personalized parameter values were estimated from the data by minimising the cost function $C(\theta)$ using *lsqnonlin* (MATLAB 2019b, The MathWorks Inc., Natick, Massachusetts, the United States) a local, gradient-based solver.

$$C(\boldsymbol{\theta}) = \sum_{i=1}^{M}\sum_{j=1}^{T_i}\left(\frac{y_{i,j}(\boldsymbol{\theta}) - y_{i,j}^{obs}}{\max\left(y_i^{obs}\right)}\right)^2 + \left(AUC_G|_{240} - G_{meal}\right) + \left(AUC_{TG}|_{600} - TG_{meal}\right) + \left(TG_{PL}|_{720} - TG_b\right) + \left(NEFA_{PL}|_0 - NEFA_b\right)$$

Where the cost function $C(\boldsymbol{\theta})$ is composed of the sum of squared error between $y_{i,j}(\boldsymbol{\theta})$ the model simulation for a parameter set $\boldsymbol{\theta}$ and $y_{i,j}^{obs}$ the measures plasma concentration of metabolite i and time point j and a number of terms to penalised physiologically undesirable behaviors such as nutrient dumping or a failure to return to the measured fasting state following the meal.[28] These additional penalties have been dubbed physiology-informed learning. To tailor the model to an individual, basal glucose and insulin values are fixed to the measured fasting values as recommended in Maas et al.[45] The volume of distribution of meal derived glucose and triglyceride is defined as a function of body-weight measured in kg in accordance with the formula proposed by Lemmens et al.[54] The carbohydrate and lipid content of the ingested meal are supplied to the Mixed Meal Model in mg. Finally, to prevent the optimisation algorithm from becoming trapped in erroneous local minima, personalized parameter sets were defined as the parameter set with the lowest error measured using the cost function $C(\boldsymbol{\theta})$ obtained following five initializations of the optimization algorithm using Latin hypercube sampling of the solution space.

The MATLAB code to generate and visualise personalized Mixed Meal Models is provided in Supplemental Folder S1. Moreover, the Mixed Meal Calculator located in Supplemental Folder S2 provides an implementation of the Mixed Meal Model in a stand-alone application with a graphical-user interface allowing meal challenge test data to be entered in order to generate a personalized model without the need for a MATLAB license. Both the Mixed Meal Model code and Mixed Meal Calculator can also be downloaded from https://github.com/shauna-odonovan.

Personalized parameter estimates were compared to independent measures of health using Spearman rank correlation using the *corr* function in MATLAB. Personalized parameter estimates are z-normalised before principal component analysis is performed using the *pca* function in MATLAB. The resulting PCA scores and loadings are visualised using the *biplot* function.

ADDITIONAL RESOURCES

Meal response data for people with overweight and obesity from three nutritional internvetion studies were used in this analysis. The NutriTech Study was registered on the International Clinical Trials Register at https://clinicaltrials.gov/study/NCT01684917. The MetFlex Study was registered on the International Clinical Trials Register at https://clinicaltrials.gov/study/NCT02519127. The BellyFat Study was registered on the Internation Clinical Trials Registry at https://clinicaltrials.gov/study/NCT02194504.