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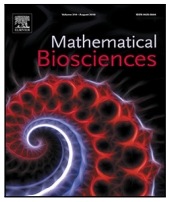

Original Research Article

# Modelling remission from overweight type 2 diabetes reveals how altering advice may counter relapse

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ABSTRACT

The development or remission of diet-induced overweight type 2 diabetes involves many biological changes which occur over very different timescales. Remission, defined by $HbA_{1c} < 6.5\%$, or fasting plasma glucose concentration $G < 126$ mg/dl, may be achieved rapidly by following weight loss guidelines. However, remission is often short-term, followed by relapse. Mathematical modelling provides a way of investigating a typical situation, in which patients are advised to lose weight and then maintain fat mass, a slow variable. Remission followed by relapse, in a modelling sense, is equivalent to changing from a remission trajectory with steady state $G < 126$ mg/dl, to a relapse trajectory with steady state $G \geq 126$ mg/dl. Modelling predicts that a trajectory which maintains weight will be a relapse trajectory, if the fat mass chosen is too high, the threshold being dependent on the lipid to carbohydrate ratio of the diet. Modelling takes into account the effects of hepatic and pancreatic lipid on hepatic insulin sensitivity and $\beta$-cell function, respectively. This study leads to the suggestion that type 2 diabetes remission guidelines be given in terms of model parameters, not variables; that is, the patient should adhere to a given nutrition and exercise plan, rather than achieve a certain subset of variable values. The model predicts that calorie restriction, not weight loss, initiates remission from type 2 diabetes; and that advice of the form 'adhere to the diet and exercise plan' rather than 'achieve a certain weight loss' may help counter relapse.

## 1. Introduction

Exciting new developments in the treatment of type 2 diabetes by nutrition and exercise alone have been gaining attention. The two-year results of the Diabetes remission clinical trial (DiRECT) show that weight loss can put type 2 diabetes into remission for at least two years [1]. In this randomised clinical trial, patients with type 2 diabetes were advised to lose weight by following a liquid low-calorie diet. After one year, 68/149 (46%) of the patients in the intervention group were in remission, defined by $HbA_{1c} < 6.5\%$. This figure reduced to 53/149 (36%) after two years. The DiRECT study was designed to answer a number of questions including whether remission from type 2 diabetes can be durable. This article addresses the durability of remission from overweight type 2 diabetes from a modelling perspective: given certain weight loss advice, is remission predicted, and if so, how durable is it predicted to be? If subsequent relapse is predicted, how could it be prevented?

Other questions could be asked. For example, is it reasonable to assume that, since fasting plasma levels of glucose, insulin and very-low-density-lipoprotein triglyceride (VLDL-TG) are healthy, and have been healthy and stable for a few weeks or months on a new diet, that the current fat mass is also healthy? A healthy fat mass is considered to be one which is stable over time, concurrent with healthy values of other measures of well-being (for example, fasting plasma levels of glucose, insulin and VLDL-TG). Health professionals frequently advise overweight patients with type 2 diabetes to lose weight and then maintain fat mass [2–7]. Is this good advice? How much weight loss is sufficient? Is this the right question to be asking? How can one tell if the chosen diet is likely to be successful with respect to remission after only a few weeks? Modelling sheds light on these issues.

Simulations enable the comparison of three kinds of recovery advice. The first kind is based on a low-energy initial phase followed by a long-term weight maintaining phase. The second kind is based on a low-energy initial phase followed by a long-term moderate-energy diet. The third kind is based on following a moderate-energy diet in the long term. A moderate-energy diet is assumed to match the energy requirements of the individual and is predicted to lead to a healthy steady state. Previous work by the author [8] comparing the speed of high-carbohydrate low-fat diets to the speed of low-carbohydrate high-fat diets, with respect to weight loss for the overweight, can be applied to help optimise advice.

It is thought that excess lipid in the liver and excess lipid in the pancreas contribute to a loss of hepatic insulin sensitivity and to a loss

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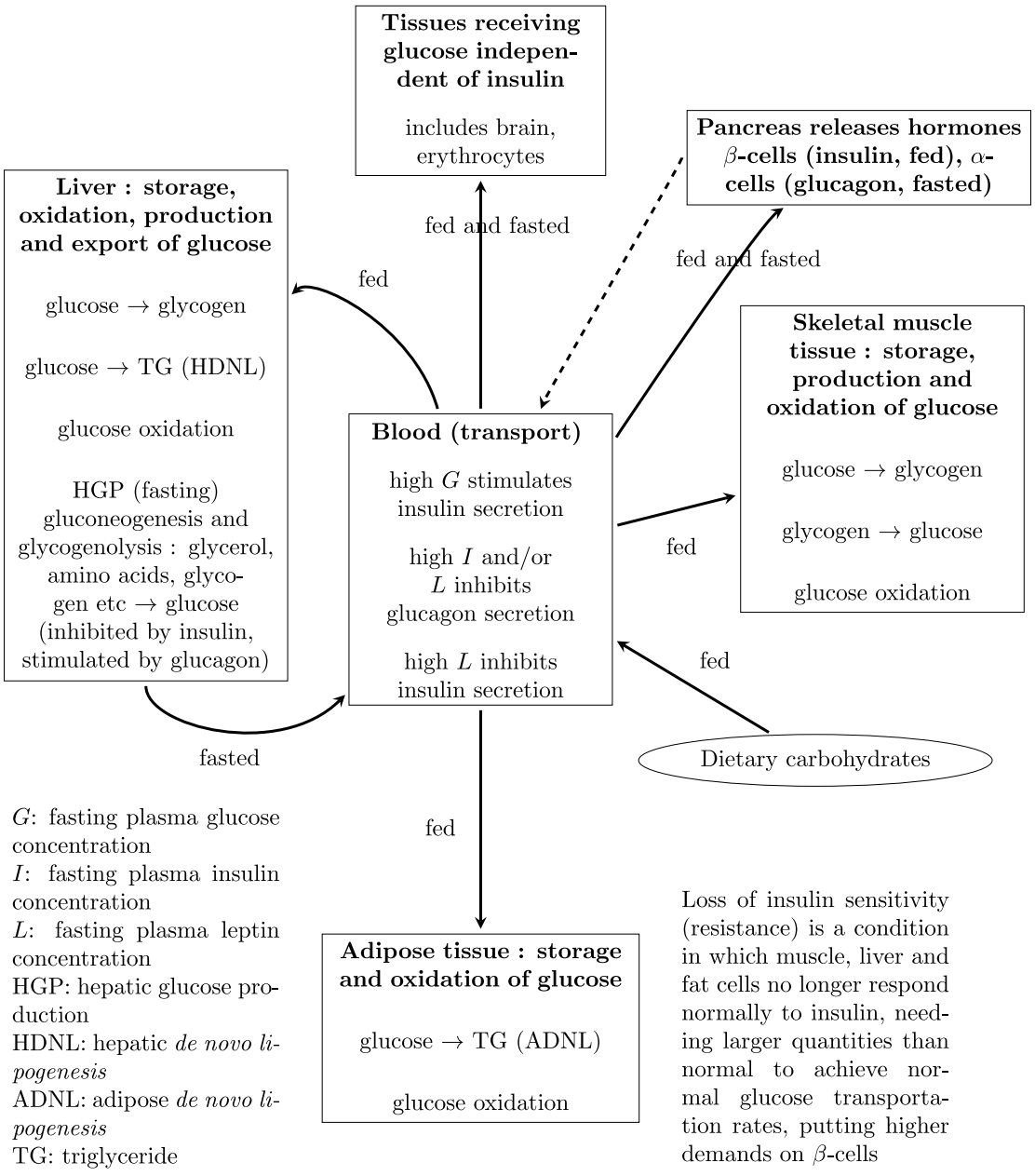



**Fig. 1.** Path of glucose through the body, dotted line denotes path of hormones from pancreas.

of $\beta$-cell function, respectively. Both of these changes lead to increases in fasting plasma glucose levels, on different timescales, hepatic insulin sensitivity and consequently hepatic glucose production changing much faster than $\beta$-cell function. Losing this extra lipid can reverse these changes and enable remission [9–11]. In this study, an original mathematical model of diabetes and lipid metabolism, developed by the author [8], which takes into account the effects of excess liver and pancreatic fat on hepatic insulin sensitivity and $\beta$-cell function respectively, is adapted to investigate remission and relapse. Diet-dependent trajectories to type 2 diabetes and to health are plotted. Choosing a diet corresponds to choosing model parameters. The model has eleven variables, including fat mass, hepatic lipid, pancreatic lipid, and fasting plasma concentrations of glucose, insulin and VLDL-TG. An advantage of modelling is that it provides insight into timing and cause and effect. These issues are difficult to explore experimentally. The model predicts the durability of remission or relapse in different scenarios. Model predictions provide a basis for altering advice to counter relapse.

Values of $HbA_{1c}$ are not simulated in this study. Instead, $G < 126$ mg/dl is used to define remission from diabetes. It is assumed that values of $G < 126$ mg/dl maintained for the previous three months should correspond to healthy $HbA_{1c}$ measurements.

## 2. Glucose and lipid metabolism and the twin cycle hypothesis

Aspects of glucose and lipid metabolism included in the model are summarised in Figs. 1 and 2. The path of glucose through the body is shown schematically in Fig. 1. Dietary carbohydrates appear in the blood after meals and are transported with the help of insulin into the liver and skeletal muscle cells for fuel or storage as glycogen, into the adipose tissue for conversion to triglyceride (TG) or oxidation and into some tissues independently of insulin. The path of lipids through the body is shown schematically in Fig. 2. Dietary TG is transported in blood as chylomicron triglyceride (CM-TG). At the cell boundary, a TG molecule lipolyses into three non-esterified fatty acids (NEFA) and a glycerol molecule, when entering or leaving the adipose, muscle or

**Table 1**
Model variables (fasting).

| Variable | Symbol | Units | |
|---|---|---|---|
| Plasma glucose concentration | $G$ | mg/dl | |
| Plasma insulin concentration | $I$ | ng/ml | Secreted by $\beta$-cells |
| $\beta$-cell mass | $\beta$ | mg | |
| Plasma leptin concentration | $L$ | ng/ml | Secreted by adipocytes |
| Fat mass | $F$ | kg | Mass of adipocytes |
| Plasma glucagon concentration | $Gg$ | pg/ml | Secreted by $\alpha$-cells |
| Plasma non-esterified fatty acids | NEFA | mg TG/dl | |
| Hepatic lipid | HLipid | mg TG/dl | |
| Muscle lipid | MLipid | mg TG/dl | |
| Very-low-density-lipoprotein triglyceride | VLDL-TG | mg TG/dl | Secreted by the liver |
| Pancreatic lipid | PLipid | mg TG/dl | |

hepatic tissue. The liver makes VLDL-TG for export, fuel for muscle and adipose tissue. The parameters used to model the diets are the rate of carbohydrate intake (CHOin) and the rate of dietary lipid intake (TGin). The TG lipolysis rate ($r_{Ll}$) and the lipid oxidation rate ($r_{Lox}$) are defined in terms of CHOin [8,12]. See Appendix C.

It is assumed that dietary carbohydrate, if available, is oxidised for fuel in preference to dietary lipid and that, over one day, most dietary carbohydrate intake is oxidised [13]. Moreover, daily dietary carbohydrate intake is assumed to match daily dietary carbohydrate disposal; through oxidation, conversion to glycogen or conversion to lipid. See Section 3.4 for more detail.

The model was formulated with the twin cycle hypothesis [9,14,15] in mind, but has simpler assumptions. The twin cycle hypothesis proposes that diets of excess energy will cause lipid stores to grow. Excess hepatic lipid is thought to cause a loss of hepatic insulin sensitivity, resulting in increased hepatic glucose production (HGP) [14–16]. Excess pancreatic lipid, accumulated once hepatic stores have grown, is thought to cause a loss of $\beta$-cell function, due to dedifferentiation of these cells [17–19]. Reducing excess lipid in the liver and pancreas is thought to enable an improvement in hepatic insulin sensitivity and consequently a reduction in HGP, and to enable the redifferentiation of $\beta$-cells and the consequent improvement of insulin secretion, although the latter may be less successful in those who have had type 2 diabetes for many years [4]. In the model, hepatic and pancreatic lipids increase concurrently and rapidly on a diet of excess energy. The effects of excess lipid in the liver are rapid, reducing hepatic insulin sensitivity and hence increasing HGP, as seen in an overfeeding experiment [12]. The effects of excess lipid in the pancreas take much longer to show as $\beta$-cell dedifferentiation, as seen in the DiRECT trial [11].

## 3. The dynamical systems model

### 3.1. Variables

Interactions between the eleven variables listed in Table 1 are modelled. It is assumed that all biomarkers are measured at fasting. Typical variable values are listed in Table 2, assuming a healthy person with a lean body mass of 60 kg with approximately 20% body mass as adipose tissue [20]. The differential equations are similar to those found in the original model [8], but they have been updated. Small adjustments were made in order to obtain lower VLDL-TG at higher fat masses, at steady state (Section 3.16). The initial aim was to produce trajectories from health with variable values at five to six years consistent with the DiRECT trial baseline characteristics [1], yielding a starting point for this study in remission and relapse.

### 3.2. Parameters - dietary

Diets are represented by carbohydrate, lipid and protein intake. Protein intake is assumed to be fixed and moderate in all the diets investigated, except for the low-energy diet. The rate of carbohydrate intake (CHOin), the rate of lipid intake (TGin) and the rate of protein intake are given as daily rates in Table 3, for the five diets considered.

Diets of low, moderate and high energy are considered in this study. Three isocaloric diets of moderate energy (ME) are considered, a moderate-carbohydrate moderate-fat (MCMF) diet, a high-carbohydrate low-fat (HCLF) diet and a low-carbohydrate high-fat (LCHF) diet. Moderate-energy diets are assumed to be matched to the energy requirements of an individual. Assuming a healthy starting point, simulations show that higher energy diets give trajectories to weight gain and, depending on macronutrient composition, may lead to type 2 diabetes [8, Fig 8]. In this study, the high-carbohydrate moderately-high-fat (HCMHF) diet was found to be an appropriate choice for a weight gain trajectory, yielding variable values consistent with the DiRECT data, after six years from a healthy starting point (the MCMF steady state). The HCMHF diet is a high energy (HE) diet. The low energy (LE) diet represents the weight loss diet in the DiRECT study.

The parameters CHOin, $\text{CHOin}_0$ and TGin are used in the model. $\text{CHOin}_0$ is a reference value for CHOin and $\text{CHOin}_0$ will vary from person to person and with exercise habits. The value $\text{CHOin}_0 = 260$ g/d was chosen assuming a person with a lean body mass of 60 kg and moderate exercise habits. Insulin sensitivities, leptin sensitivity, the rate of lipid oxidation, the rate of lipolysis and the length of the fed state are all assumed to depend on the ratio

$$y_{\text{CHO}} = \frac{\text{CHOin}}{\text{CHOin}_0}.$$

See Appendix A–Appendix C. Low energy diets are deemed to be unsustainable, to be followed in the short term. Diets of at least moderate energy are described as sustainable.

### 3.3. Parameters - non-dietary

The model parameter values were chosen by experimentation (simulation) to give sensible steady state values with respect to a wide range of published data. Functional dependencies were chosen to reflect observed biological dependencies reported in the literature. For each such biological dependency, the chosen function had the simplest form of all those considered, since model behaviour was observed to be independent of the choice. The focus is on predicting general behaviour and trends. Reference parameter values are given in Table 2 and variable values at the reference MCMF stable steady state are given in Table 4. Published clinical estimates for insulin sensitivity $S_I = PS_I$ have been collated [8].

### 3.4. Fed and fasting terms in the differential equations

The aim is to develop a long term model, using fasting biomarker values, but of course, the fed state needs to be taken into account. Protein intake and metabolism are not modelled. Protein intake is assumed to be fixed and moderate. Modelling changes in protein intake is future work.

Carbohydrate (CHO) and lipid intake are taken into account, represented by parameters CHOin and TGin, respectively. They are treated differently, in that it is assumed that dietary carbohydrate, if available,

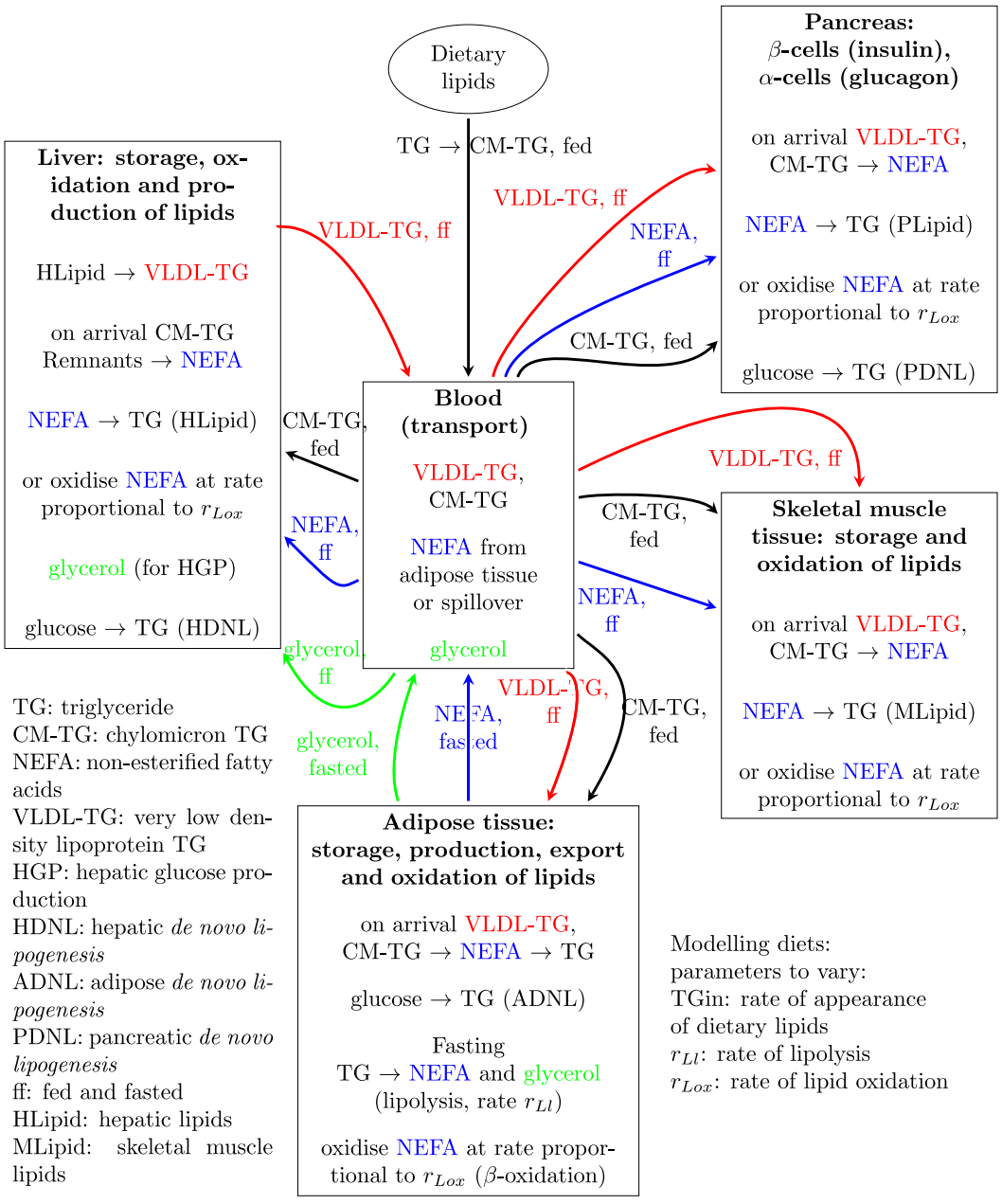



**Fig. 2.** Path of lipids and glycerol through the body.

is oxidised for fuel in preference to dietary lipid [12,13] and that most dietary carbohydrate is oxidised, although this could make for a long fed state and a short fast, in times of excess. In the model, fasting is taken to describe a state of mainly lipid oxidation, as opposed to the fed state during which dietary carbohydrate is transported into cells and oxidised, and plasma insulin peaks after meals. Hence a large proportion of the day maybe considered a fasted state for a fat-adapted subject on a LCHF or ketogenic diet. Glycogen storage is assumed to saturate quickly in times of excess and is not modelled. The rest of the daily dietary carbohydrate intake is stored as lipid (hepatic, adipose and pancreatic *de novo lipogenesis*, HDNL, ADNL and PDNL) or remains in the blood. Since daily dietary carbohydrate intake is assumed to match daily dietary carbohydrate disposal, carbohydrate intake and oxidation terms do not appear in the equations, although the carbohydrate conversion to lipid terms (HDNL, ADNL and PDNL) appear in the lipid equations. Lipid intake (TGin) and lipid oxidation must be included as they are not assumed to cancel over one day. In other words, the daily dietary carbohydrate input is assumed to equal the daily dietary carbohydrate output and since the daily dietary (fed) carbohydrate terms add to zero over one day, they are omitted. This is not so for lipids. However, the amount of CHO entering and leaving the system daily is assumed to have a profound effect on lipid oxidation rates and lipolysis [12], the length of the fed state (hours of the day delivering dietary glucose to cells with the help of insulin), leptin sensitivity [36–39], insulin sensitivity [12] and VLDL-TG clearance [26]. All of these factors combine to help determine the balance of lipids in various tissues.

What is the evidence for this approach? Short-term alterations in carbohydrate energy intake in humans have been reported [12]. In this study, the metabolic response to six dietary phases was quantified, each phase lasting five days. The diets ranged from 50% excess CHO, to 50% deficient CHO, to 50% excess lipid. The reported effects of changing dietary carbohydrate and lipid on HGP, the rate of lipid oxidation and the rate of lipolysis have been incorporated into the model. It was concluded that "altered CHO intake alters HGP specifically, and in a dose-dependent manner, and that HGP may mediate the effects

**Table 2**
Reference parameter values.

| Parameter | Value | Units | Description |
|---|---|---|---|
| $HGP_0$ | 225.0 | mg/dl/h | Basal hepatic glucose production (Section 3.5, [21]) |
| KGP | 25.0 | mg/dl/h | Kidney glucose production (Section 3.5, [21]) |
| $U_0$ | 187.5 | mg/dl/h | Insulin-independent glucose uptake (Section 3.5, [21]) |
| $E_{G0}$ | 0.06 | per h | Glucose effectiveness at zero insulin (Section 3.5, [22]) |
| $PS_I = S_I$ | 1.82 | per h per ng/ml | Skeletal muscle (peripheral) insulin sensitivity index (Section 3.5, [22–24]) |
| $HS_I$ | 1.0 | | Hepatocyte insulin sensitivity index |
| $AS_I$ | 1.0 | | Adipocyte insulin sensitivity index |
| $ACS_I$ | 1.0 | | $\alpha$-cell insulin sensitivity index |
| $S_L$ | 1.0 | | Leptin sensitivity |
| $I_0$ | 0.3 | ng/ml | Typical healthy plasma insulin concentration [25] |
| $Gg_0$ | 80 | pg/ml | Typical healthy plasma glucagon concentration [25] |
| $L_0$ | 7 | ng/ml | Typical healthy plasma leptin concentration [25] |
| $F_0$ | 15 | kg | Typical healthy fat mass [20,26] |
| $G_0$ | 75 | mg/dl | Typical healthy plasma glucose concentration, WHO |
| $NEFA_0$ | 13.44 | mg TG/dl | Typical healthy fasting plasma NEFA concentration |
| $HLipid_0$ | 1.39 | g TG/dl | Typical healthy hepatic lipid (50 g TG per 36 dl) |
| $MLipid_0$ | 8.333 | g TG/dl | Typical healthy skeletal muscle lipid (300 g TG per 36 dl) |
| $PLipid_0$ | 0.417 | mg TG/dl | Typical healthy pancreatic lipid |
| $VLDL\text{-}TG_0$ | 100 | mg TG/dl | Typical healthy fasting plasma VLDL-TG level [26] |
| LBM | 60 | kg | Lean body mass |
| CHOin | 260 | g/d | Rate of carbohydrate intake per day, will vary |
| $CHOin_0$ | 260 | g/d | Reference value for CHOin |
| TGin | 114 | g/d | Rate of trigyceride/lipid intake per day, will vary |
| $TGin_0$ | 231.5 | mg TG/dl/h | Reference dietary TG intake, 100 g per day (12 fasting h), 36 dl plasma |
| $\lambda_I$ | 8.33 | per h | Insulin decay constant [27] |
| $I_{in}$ | 0.0 | ng/ml/h | Exogenous insulin intake |
| $\sigma_r$ | 20 | ng/h/(mg $\beta$-cells) | Insulin secretion rate per mg $\beta$-cells (Section 3.6, [22]) |
| $V_{p,LBM}$ | 60 | ml/kg | Volume of plasma per kg LBM |
| $r_0$, $d_0$ | $2.5 \times 10^{-4}$ | per h | Replication and death rate of $\beta$-cells [28], 0.6% $d^{-1}$ Section 3.8 |
| $h_L$ | 0.417 | h | Plasma leptin half-life [27] |
| $r_L$ | 13.33 | ng/ml/h | Leptin secretion rate [27] |
| $k_L$ | 0.8 | | Scaling factor |
| $\lambda_{Gg}$ | 4.17 | per h | Glucagon decay constant, half-life of 8–18 min [29] |
| $\sigma_{Gg}$ | 333 | pg/ml/h | Glucagon secretion rate (Section 3.7) |
| $r_{VLDLTGpfast}$ | 27.78 | mg/dl/h | 12 g per 12 h per 36 dl i.e. 1000/36 = 27.78 mg/dl/h |
| $k_{VLDLTGpfast}$ | 0.2773 | per h | Fasting decay constant, assumes a half-life of 2.5 h [30] |
| $k_{NEFApfast}$ | 10.9 | per h | Decay constant, NEFA half-life 3.8 min [30–32] |
| $r_{Ll}$ | 152.8 | mg/dl/h | Lipolysis rate, 66 g TG equivalent per day (12 fasting h) [33] |
| $r_{Lox}$ | 1.0 | | Scales the lipid oxidation rates |
| $c$ | $6.0 \times 10^{-7}$ | | Conversion factor, mg TG per dl to kg TG per kg LBM |
| $r_{ADNL}$ | 2.315 | mg/dl/h | Rate of ADNL, see Section 3.11, 1 g per day [34] |
| $ATG_{ox}$ | 9.26 | mg/dl/h | Adipose TG oxidation rate, 4 g per day |
| $r_{HDNL}$ | 2.315 | mg/dl/h | Hepatic *de novo lipogenesis* (DNL), 1 g per day [35] |
| $r_{PDNL}$ | $3.86 \times 10^{-4}$ | mg/dl/h | Pancreatic DNL, see Section 3.15 |
| $h_{MLipid}$ | 40 | h | MLipid half-life, see Section 3.14 |
| $k_{CHO}$ | 1.1 | | Effect of dietary CHO on VLDL-TG clearance |

**Table 3**
Dietary parameters.

| Parameter | HCLF | MCMF reference | LCHF | HCMHF (HE) weight gain | LE weight loss |
|---|---|---|---|---|---|
| CHOin (g/d) | 400 | 260 | 120 | 400 | 91.4 |
| CHOin (kcal/d) | 1600 | 1040 | 480 | 1600 | 365 |
| CHOin % energy | 64.9% | 42.2% | 19.5% | 48.4% | 43.0% |
| TGin (mg/dl) | 51.8 | 114 | 176 | 145 | 19 |
| TGin (kcal/d) | 466 | 1026 | 1586 | 1306 | 171 |
| TGin % energy | 18.9% | 41.6% | 64.3% | 39.5% | 20.1% |
| protein (g/d) | 100 | 100 | 100 | 100 | 78.4 |
| protein (kcal/d) | 400 | 400 | 400 | 400 | 313 |
| protein % energy | 16.2% | 16.2% | 16.2% | 12.1% | 36.9% |
| total kcal/d | 2466 | 2466 | 2466 | 3306 | 850 |

of CHO on whole body fuel selection both by providing substrate and by altering serum insulin concentrations, and that altered lipolysis and tissue oxidation efficiency contribute to changes in fat oxidation, and that surplus CHO is not substantially converted by the liver to fat as it spares fat oxidation, but that fractional DNL may nevertheless be a qualitative marker of recent CHO intake." As HGP rises, so does whole body CHO oxidation [12]. In the model, it is assumed that excess dietary CHO lowers hepatic insulin sensitivity and hence increases HGP as reported, over a few days. HGP did not respond to increases in dietary lipid in the experiments and so no such effect was modelled. In addition, the results in this study [12] were used to derive the dose-dependent effects of excess or deficient CHO on lipolysis and lipid oxidation rates. It was also noted that, even on high CHO diets, less than 5 g lipid per day could be attributed to HDNL. In the model, HDNL has been kept low to reflect this.

Excess dietary CHO is thought to cause fasting plasma insulin levels to rise, a form of insulin resistance or loss of sensitivity, see A. Excess dietary CHO is also thought to cause lipid levels to rise in organs due to lower lipid oxidation rates and the sparing of lipid stores [12]. Higher hepatic lipid levels are thought to cause lower hepatic insulin sensitivity [14–16], and hence higher fasting HGP [12].

Per day, a fed state of twelve hours and a fasted state of twelve hours are assumed, for the reference mixed MCMF diet. Per day, integration is carried out over these twelve fasting hours. However, the durations of the fed and fasted states are assumed to be dependent on CHOin. Hence, the sizes of the fed and fasted terms are scaled according to CHOin. Let $f_{\text{fast}}$ be the fasted (or fasting) scaling term and let $f_{\text{fed}}$ be the fed scaling term. An equation was found that modelled an increase in fasting hours (from 12 to approximately 14) for the LC diets (120 g/d CHO) and that modelled a decrease in fasting hours (from 12 to approximately 10) for the HC diets (400 g/d CHO). These times are consistent with the reported variations in fed and fasted hours [40,41].

The equation for $f_{\text{fast}}$, given below, fulfils this requirement and has a simple form.

Let $a_{\text{CHO}} > 0$ be a scaling term, set to 3.0 and recall $\text{CHOin}_0$ is a moderate reference carbohydrate intake. Let

$$x_{\text{CHO}} = 1 + \frac{\text{CHOin} - \text{CHOin}_0}{a_{\text{CHO}} \times \text{CHOin}_0}, \tag{1}$$

let

$$f_{\text{fast}} = \frac{2}{1 + x_{\text{CHO}}^2} \tag{2}$$

and let $f_{\text{fed}} = 2 - f_{\text{fast}}$. The fasting time is 12 h, scaled by $f_{\text{fast}}$, and the fed time is 12 h, scaled by $f_{\text{fed}}$. Higher values of $f_{\text{fast}}$ correspond to lower carbohydrate diets. Recall that the fed terms in the equations always relate to changes in lipid content, since the fed terms relating to changes in dietary carbohydrate (intake, oxidation and conversion to lipid) are assumed to cancel over one day and are hence omitted, save for the DNL terms in the lipid equations.

### 3.5. The rate of change of plasma glucose concentration

The rate of change of plasma glucose concentration is modelled by

$$\begin{aligned}\frac{dG}{dt} = f_{\text{fast}}\Big(&\text{HGP}(I, Gg, L, \text{HLipid}) + \text{KGP} - U_0 \\ &- E_{G0}\Big(\frac{(S_L f_{S_L}\tilde{g}(t)L)^2}{(S_L f_{S_L}\tilde{g}(t)L)^2 + \frac{3}{7}{L_0}^2} + 0.3\Big)G \\ &- 0.7PS_I f_{PS_I}\tilde{g}(t)I(f_{\text{Lep+}} + 0.5)G \\ &- 0.3AS_I PS_I f_{AS_I}\tilde{g}(t)I(f_{\text{Lep-}} + 0.5)\frac{F}{F_0}G\Big).\end{aligned} \tag{3}$$

The first three terms represent hepatic glucose production (HGP, production from the liver at fasting), kidney glucose production (KGP) and $U_0$ (insulin-independent uptake, includes disposal to the brain and erythrocytes). The fourth term represents glucose effectiveness ($E_{G0}$) [22], dependent on leptin [42]. The insulin-dependent terms represent skeletal muscle (peripheral) uptake and adipocyte uptake, respectively, at fasting, modulated by leptin. The product $S_L f_{S_L}\tilde{g}(t)$ represents leptin sensitivity, $PS_I f_{PS_I}\tilde{g}(t)$ represents peripheral insulin sensitivity and $AS_I f_{AS_I}\tilde{g}(t)$ represents adipose insulin sensitivity. The terms $S_L$, $AS_I$ and $PS_I$ have a reference values equal to 1, 1 and 1.82, respectively, Sensitivity terms $f_{S_L}$, $f_{PS_I}$ and $f_{AS_I}$ are defined in Appendix A, dependent on VLDL-TG and $F$, MLipid, and $L$, respectively. The scaling of the last two terms represents 70% insulin-dependent disposal to peripheral tissue and 30% to adipose tissue, given reference parameters. The term $\tilde{g}(t)$ models the dependency of leptin and insulin sensitivities on parameter CHOin, adjusting over a few weeks from a previous carbohydrate intake, defined in Appendix B, with a reference value of one.

The equation for HGP is

$$\text{HGP} = \text{HGP}_0 \times f_{\text{HGP},I} \times f_{\text{HGP},Gg} \times f_{\text{HGP},L}. \tag{4}$$

The product $HS_I f_{HS_I}\tilde{g}(t)$ represents hepatic insulin sensitivity. Each of the three terms has a reference value of one. The term $f_{HS_I}$ depends on HLipid, see Appendix A. The combined term $HS_I(t)f_{HS_I}\tilde{g}(t)I$ represents the effective plasma insulin concentration detected by the liver.

Since hyperinsulinemia inhibits HGP (see [21], p801), the dependence of HGP on effective plasma insulin concentration was modelled by a decreasing sigmoid, chosen so that its minimum value is approximately one half (at high but realistic fasting values of effective plasma insulin concentration, for example, nearly twice the reference value); and so that at the reference stable steady state, its value is one. The insulin (and HLipid) dependence was modelled by

$$f_{\text{HGP},I} = f_{\text{HGP},I}(I, \text{HLipid}) = \frac{7}{4}\left(\frac{(\frac{4}{3})I_0{}^2}{(\frac{4}{3})I_0{}^2 + (HS_I f_{HS_I}\tilde{g}(t)I)^2}\right) \tag{5}$$

The glucagon dependence was set to

$$f_{\text{HGP},Gg}(Gg) = \frac{Gg^2}{Gg^2 + Gg_0^2} + 0.5, \tag{6}$$

where $Gg_0 = 80$ pg/ml is a normal healthy value at fasting [25]. Then $f_{\text{HGP},Gg}(0) = 0.5$, $f_{\text{HGP},Gg}(80) = 1.0$ and $\lim_{Gg\to\infty} f_{\text{HGP},Gg}(Gg) = 1.5$. Leptin has both stimulating and inhibiting influences in glucose homeostasis. The function

$$f_{\text{Lep+}} = f_{\text{Lep+}}(L, F, \text{VLDL-TG}) = \frac{(S_L f_{S_L}\tilde{g}(t)L)^2}{(S_L f_{S_L}\tilde{g}(t)L)^2 + L_0^2} \tag{7}$$

models stimulation and

$$f_{\text{Lep-}} = f_{\text{Lep-}}(L, F, \text{VLDL-TG}) = \frac{L_0^2}{(S_L f_{S_L}\tilde{g}(t)L)^2 + L_0^2} \tag{8}$$

models inhibition. The leptin inhibition on HGP is modelled by

$$f_{\text{HGP},L} = f_{\text{Lep-}} + 0.5, \tag{9}$$

see [43, Fig. 3]. The dependence on the parameters CHOin and $\text{CHOin}_0$ via $\tilde{g}(t)$ has been omitted for brevity in the equations. For further biological justification see earlier models [8,22].

### 3.6. The rate of change of plasma insulin concentration

Insulin is secreted by the pancreatic $\beta$-cells in response to raised levels of $G$. The mass of the differentiated insulin-secreting pancreatic $\beta$-cells in mg was denoted by $\beta$. The amount of insulin secreted by one mg of $\beta$-cells per hour was denoted by $\sigma$. It was assumed that the adult human $\beta$-cell mass is 1–2 g [44], varying in proportional to lean body mass (LBM) in healthy non-diabetics. It was also assumed that plasma volume ($V_p$) could be expected to rise in proportion to LBM [45].

The rate of change of $I$ was modelled by

$$\frac{dI}{dt} = f_{\text{fast}}\left(\frac{\beta\sigma}{V_p} - \lambda_I I\right). \tag{10}$$

where

$$\sigma = \sigma_r(f_{\text{Lep-}} + 0.5)\frac{G^2}{\alpha_{GI}^2 + G^2}. \tag{11}$$

To represent the effect of $G$, the insulin secretion term $\sigma_r$ was multiplied by an increasing sigmoid function, setting $\alpha_{GI} = 140$ mg/dl [22], with a value of 0.25 at $G = 80$. The term $(f_{\text{Lep-}} + 0.5)$ models the inhibition of leptin on insulin secretion [46]. Let $\lambda_I$ per hour be the decay constant for insulin, then the half-life of insulin is $(\ln(2))/\lambda_I$ in hours. Since the half-life of insulin in plasma is 4–6 min in humans [27], the value $\lambda_I = 8.33$ per hour was chosen. Assuming steady state, setting $G = 80$ and $L = L_0 = 7$, $f_{\text{Lep-}} = 0.5$, $V_p = 36$ dl, $I = 0.3$ ng/ml and $\beta = 1800$ mg, a healthy fasting value of $\sigma_r = 20$ ng insulin/hour/mg $\beta$-cells may be estimated.

The value $I = 7.1$ $\mu$ IU/ml, that is $I = 52$ pM or $I = 0.30$ ng/ml was considered to be a normal healthy value for fasting plasma insulin concentration in adult humans [25,47] and $I_0 = 0.3$ ng/ml was taken to be the reference value. Fasting insulin plasma concentration in non-diabetics was found to fall in the range 0.1–0.9 ng/ml [48].

### 3.7. The rate of change of plasma glucagon concentration

Glucagon is a hormone secreted by the $\alpha$-cells of the pancreas, instrumental in controlling plasma glucose concentration, via its action on the liver. Plasma glucose concentration was thought to be the most important regulator of glucagon secretion, where low $G$ stimulates secretion and high $G$ inhibits [49]. However, this action may be indirect, through hormones. There is evidence that high pancreatic insulin concentration inhibits glucagon secretion; that high leptin concentration, induced by either subcutaneous infusion or infusion into the intracerebral ventricle, suppresses glucagon secretion; and that a lack of both

hormones may cause glucagon hypersecretion [50]. The simulation results in this study were obtained by modelling a dependence of glucagon secretion inhibition on pancreatic insulin concentration and plasma leptin concentration. Since pancreatic insulin concentrations are hard to measure, plasma concentrations were used, assuming no exogenous insulin. The mass of $\alpha$-cells was assumed to be constant. The rate of change of plasma glucagon concentration was modelled by

$$\frac{dGg}{dt} = f_{\text{fast}}\left(2\sigma_{Gg}\frac{I_0^2}{I_0^2 + (ACS_I f_{ACS_I}\tilde{g}(t)I)^2}(f_{\text{Lep-}} + 0.5) - \lambda_{Gg}Gg\right), \quad (12)$$

as a product of decreasing sigmoids in $I$ and $L$, plus a decay term. Here $\sigma_{Gg}$ denotes the secretion rate of glucagon from the $\alpha$-cells (in pg/ml/hour), $\lambda_{Gg}$ (per hour) is the decay constant for glucagon in plasma and $ACS_I f_{ACS_I}\tilde{g}(t)$ represents $\alpha$-cell insulin sensitivity. The term $ACS_I$ has a reference value equal to one. The sensitivity term $f_{ACS_I}$ is defined in Appendix A, dependent on PLipid.

At steady state $dGg/dt$ is zero, and so by substituting normal healthy values $I = I_0$, $L = L_0$, $Gg = Gg_0 = 80$ pg/ml [25,50], and assuming the half-life of glucagon in plasma to be 10 min (based on published information [29] where the observed half-life is given as 8–18 mins), reference values $\lambda_{Gg} = 4.17$ per hour and $\sigma_{Gg} = 333$ pg/ml/h were estimated.

### 3.8. The rate of change of $\beta$-cell mass

Evidence suggests high levels of pancreatic lipid may cause $\beta$-cell dedifferentiation, leading to a loss of insulin secretion [18]. Changes in diet which result in a loss of excess pancreatic lipid may in turn reverse this process [51]. Let $r_0$ and $d_0$ be the reference replication and death rate parameters, respectively. Set $r_0 = d_0 = 2.5 \times 10^{-4}$, to ensure a death rate of about 0.6% per day, consistent with the estimation of 'considerably less than 1% per day' as given in [28]. Replication (or differentiation or redifferentiation) is assumed to be enhanced by increasing $G$ unless PLipid is high. In this case, the replication (or differentiation or redifferentiation) rate falls and the death (or dedifferentiation) rate rises. Let the rate of change of $\beta$-cell mass be modelled by

$$\frac{d\beta}{dt} = \left(r_0(1.0 + f_{G\beta 1}f_{\text{PLipid}\beta 2}) - d_0(0.92 + f_{\text{PLipid}\beta 3})\right)\beta, \quad (13)$$

where

$$f_{G\beta 1} = 0.2\left(\frac{G}{G_0} - 1.0\right), \quad (14)$$

$$f_{\text{PLipid}\beta 2} = \frac{1.0 + \exp(1.0)}{1.0 + \exp\left(\frac{\text{PLipid}}{\text{PLipid}_0}\right)} \quad (15)$$

and

$$f_{\text{PLipid}\beta 3} = \frac{0.2}{1.0 + \exp\left(1.0 - \frac{\text{PLipid}}{\text{PLipid}_0}\right)}. \quad (16)$$

At a very high pancreatic lipid content, this models an increase in the dedifferentiation rate of about 12% (to $1.12d_0$) and no change in the birth or differentiation rate.

### 3.9. Interpreting $\beta$-cell mass in the model

The effective insulin secretion rate is $\beta\sigma$. In the model, a rise in $\beta$-cell mass (differentiated cells) accompanies an increased need for insulin, within the constraints of the model, that is, pancreatic lipid allowing. On a low-carbohydrate (LC) diet, the $\beta$-cell mass is lower than that for a high-carbohydrate (HC) diet, in the absence of other changes, since the insulin requirement is lower.

### 3.10. The rate of change of plasma leptin concentration

The adipoinsular axis [52] describes a negative feedback loop involving insulin, leptin and fat mass. Insulin stimulates adipogenesis, but is inhibited by leptin, which is secreted by adipocytes. It is assumed that leptin secretion is proportional to fat mass and stimulated by plasma insulin. This stimulation is modelled by

$$f_{LI} = 1.0 - \frac{k_L}{2} + \frac{k_L(AS_I f_{AS_I}\tilde{g}(t)I)^2}{(AS_I f_{AS_I}\tilde{g}(t)I)^2 + I_0^2} \quad (17)$$

where $k_L = 0.8$. Based on these assumptions, the rate of change of plasma leptin concentration is assumed to be

$$\frac{dL}{dt} = f_{\text{fast}}\left(r_L\frac{F}{F_0}f_{LI} - L\frac{\ln(2)}{h_L}\right) \quad (18)$$

where $r_L$ is a reference healthy leptin secretion rate and $h_L$ is the half-life of plasma leptin. The rate $r_L$ was estimated, based on the measurement 800 ng/person/min [27]. Assuming a person of average size with 3600 ml plasma, this converts to 800 ng/3600 ml/min or 800 ng/60 ml per hour or 13.33 ng/ml/h.

### 3.11. The rate of change of fat mass

The rate of change of fat mass includes fed and fasted terms. The rate of change of fat mass is initially derived assuming 12 hours fed and 12 hours fasting per day. Then fed and fasted terms are scaled to take account of the carbohydrate content of the diet, see Section 3.4.

Triglyceride intake into adipocytes is due to the arrival of dietary chylomicron triglyceride and VLDL-TG (fed and fasting). Adipose *do novo lipogenesis* (ADNL), inhibited by leptin and stimulated by insulin and high carbohydrate intake, also contributes to fat stores, although rates of even whole-body DNL are small, even on high carbohydrate diets, and most DNL is thought to happen in the liver [12,34]. Assuming reference parameters and variable values, the rate $r_{\text{ADNL}} = 2.315$ mg/dl/h was calculated to satisfy ADNL equal to 1 g TG per 12 h per 60 kg LBM, specifically

$$\text{ADNL} = r_{\text{ADNL}}(f_{\text{Lep-}} + 0.5)\left(\frac{y_{\text{CHO}}^2}{1 + y_{\text{CHO}}^2} + 0.5\right)\frac{AS_I f_{AS_I}\tilde{g}(t)I}{I_0}. \quad (19)$$

The rate of appearance from the liver of fasting plasma VLDL-TG (VLDLTGpfast) was estimated to be $r_{\text{VLDLTGpfast}} = 27.78$ mg/dl/h, calculated as 12 g per 12 h per 36 dl, with a half-life of 2.5 h. The rate of appearance from the liver of fed plasma VLDL-TG (VLDLTGpfed) was estimated to be $r_{\text{VLDLTGpfed}} = 18.52$ mg/dl/h, calculated as 8 g per 12 h per 36 dl, with a half-life of 4.5 h [8]. A fasting VLDL-TG mean rate of appearance of 14.9 μmol/kg/h has been reported [30]. This corresponds to 27.5 mg/dl/h, assuming the molecular weight of TG is 885 g and that a person of average size weighs 75 kg and has 36 dl plasma. Hence, the decay constant $k_{\text{VLDLTGpfast}} = \ln(2)/2.5 = 0.2773$ per h and the decay constant $k_{\text{VLDLTGpfed}} = \ln(2)/4.5 = 0.2773(2.5/4.5) = 0.1540$ per h. Let the rate of appearance of fat mass be modelled by

$$\begin{aligned} F_+ &= 0.45 \times \text{TGin} \\ &+ 0.5 f_{\text{fast}}(k_{\text{VLDLTGpfast}} k_{\text{CHO}} \text{VLDLTGpfast}) \\ &+ 0.5 f_{\text{fed}}(k_{\text{VLDLTGpfed}} k_{\text{CHO}}(1.2 \times \text{VLDLTGpfast})) \\ &+ f_{\text{fed}}\text{ADNL}. \end{aligned} \quad (20)$$

In the model, TGin is shared out in fixed proportions between organs. It is assumed that half of the circulating VLDL-TG is delivered to adipose tissue [53]. This works out to be 10 g/d when using reference parameters. The fed concentration VLDLTGpfed = 1.2 × VLDLTGpfast [8,30]. The term $k_{\text{CHO}} = 1.1$, set to achieve the baseline values of VLDL-TG seen in the DiRECT patients.

Triglyceride loss from adipocytes is modelled by the following equation

$$F_- = 0.9 r_{Ll}(t) f_{\text{fast}}(0.5 + f_{\text{Lep+}}) f_{\text{NEFAp}I}\left(\frac{1.4F^2}{F^2 + F_0^2} + 0.3\right)$$

$$+ r_{Lox}(t)\mathrm{ATG}_{ox}(0.5 + f_{\mathrm{Lep}+})\left(\frac{F}{F_0}\right)\left(f_{\mathrm{fed}}\frac{0.92}{2.15} + f_{\mathrm{fast}}\frac{1.23}{2.15}\right). \quad (21)$$

The first term represents lipolysis and depends on the lipolysis rate $r_{Ll}$ (or $r_{Ll}(t)$ when considering changing diets, see Appendix C). The factor 0.9 represents 10% recycling of lipolysed triglyceride. Inhibition by insulin [54] is modelled by

$$f_{\mathrm{NEFApI}} = \frac{I_0^2}{(AS_I f_{AS_I}\tilde{g}(t)I)^2 + I_0^2} + 0.5. \quad (22)$$

Stimulation by leptin [55,56] is modelled by $(0.5 + f_{\mathrm{Lep}+})$. Lipolysis increases with excess fat mass. A Hill function was used to model an increase that is less than proportional to increases in fat mass, at higher values of fat [57]. The second term models oxidation of TG in adipocytes. The rate $\mathrm{ATG}_{ox}$ is calculated as 4 g/d. The term $r_{Lox}$ (or $r_{Lox}(t)$ when considering changing diets, see Appendix C) is a scaling factor with reference value equal to one. Oxidation is assumed to be stimulated by leptin [58], proportional to fat mass. Fed and fasting rates of lipid oxidation were partitioned according to the rates reported in Table 1 [30]. Finally,

$$\frac{dF}{dt} = c(F_+ - F_-)\mathrm{LBM}. \quad (23)$$

This equation is worked in units of mg TG per dl plasma, converting in the final equation to kg TG per h by using the conversion factor $c = 6.0 \times 10^{-7}$ per h and multiplying by LBM.

### 3.12. The rate of change of plasma NEFA concentration

The rate of appearance of fasting plasma NEFA is due to the lipolysis of TG in adipocytes as discussed in Section 3.11. Spillover, which happens during the fed state, is not included. A mean concentration and mean rate of appearance of plasma NEFA at fasting has been reported [30], from which a decay constant of approximately 10 per h was calculated, corresponding to a half-life of about 4 min. Estimates of this half-life vary from 30–180 s [31] to 2–4 min [32]. A half-life of 3.8 min was assumed, corresponding to a fasting decay constant for plasma NEFA $k_{\mathrm{NEFApfast}} = \ln(2)60/3.8 = 10.9$ per h. The rate of change of plasma NEFA concentration was modelled by

$$\frac{d\mathrm{NEFAp}}{dt} = f_{\mathrm{fast}} r_{Ll}(t)(0.5 + f_{\mathrm{Lep}+}) f_{\mathrm{NEFApI}}\left(\frac{1.4F^2}{F^2 + F_0^2} + 0.3\right) - f_{\mathrm{fast}} k_{\mathrm{NEFApfast}}\mathrm{NEFApfast}. \quad (24)$$

It was assumed that 3.3 moles of NEFA correspond to 1 kg TG. The reference rate of lipolysis is $r_{Ll} = 152.80$ mg/dl/h which corresponds to 4.0 μmol/kg/min, assuming a person of 75 kg with 36 dl of plasma. This is close to the mean reported value of 4.2 μmol/kg/min [30]. At reference parameters, a fasting plasma NEFA concentration of 14.5 mg TG/dl, is obtained, which corresponds to 0.48 mmol/l, consistent with reported values 0.56 mmol/l [30] and 0.3–0.6 mmol/l [57].

### 3.13. The rate of change of hepatic lipids

Hepatic TG balance is summarised below. See Appendix D for more information concerning lipid balances. At reference parameters, based on experimental evidence, it was assumed that the liver daily

1. receives $0.25 \times \mathrm{TGin}$ (as CM-TG remnants), 25 g (fed) [35],
2. receives $0.22 \times 0.23 \times \mathrm{TGin}$, spillover, 5 g (fed),
3. and receives NEFA, assuming 10% recycled to adipose tissue, then 32% of the remainder is delivered to the liver, equivalent to 19 g TG (fasting) [35],
4. makes 1 g TG (HDNL) [12,35],
5. loses 20 g TG secreted on VLDL (total production of VLDL-TG in nondiabetics given as 250 mg per day per kg [59]), assuming 8 g fed and 12 g fasted [60],
6. and loses 30 g TG through $\beta$-oxidation (balances intake),
7. equating to 50 g TG in and out [61].

It was assumed that HDNL has a reference value equal to $r_{\mathrm{HDNL}} = 2.31$ mg/dl/h since this equates to 1 g TG per day. To model a noticeable effect of CHOin on HDNL, let $m_{\mathrm{HDNL}} = 8$, $b_{\mathrm{CHO}} = 0.66$ and set $k_{\mathrm{HDNL}} = 0.5\log(m_{\mathrm{HDNL}} - 1)$. Let

$$z_{\mathrm{CHO}} = \frac{\mathrm{CHOin} - \mathrm{CHOin}_0}{b_{\mathrm{CHO}} \times \mathrm{CHOin}_0} \quad (25)$$

and let

$$\mathrm{HDNL} = \frac{r_{\mathrm{HDNL}} m_{\mathrm{HDNL}}}{1 + \exp(-k_{\mathrm{HDNL}}(z_{\mathrm{CHO}} - 2))} \quad (26)$$

be a translated and scaled logistic function that increases with CHOin. This increasing function has the value 9 mg/dl/h at CHOin equal to 600 g/d with $\mathrm{CHOin}_0 = 260$ g/d; that is, about 4 g TG daily. An increase in HDNL with skeletal muscle lipids was modelled by

$$f_{\mathrm{HDNLML}} = \frac{2\mathrm{MLipid}^2}{\mathrm{MLipid}_0^2 + \mathrm{MLipid}^2} \quad (27)$$

assuming that as MLipid rises, peripheral insulin sensitivity falls, less glucose is transferred to skeletal muscle and more is delivered to the liver to be converted to TG [62]. The stimulation of HDNL by insulin was modelled by

$$f_{\mathrm{HDNLI}} = \frac{2I^2}{I^2 + I_0^2} \quad (28)$$

omitting insulin sensitivity to take account of selective hepatic insulin resistance in which hyperinsulinemia fails to suppress HGP but still promotes HDNL [62–64]. The term

$$f_{\mathrm{VLDLTGI}} = (0.33)\frac{2I_0^2}{(HS_I f_{HS_I}\tilde{g}(t)I)^2 + I_0^2} + 0.67 \quad (29)$$

models the inhibition of insulin on the secretion of VLDL-TG [65,66]. Then, including fed and fasted contributions,

$$\begin{aligned}\frac{d\mathrm{HLipid}}{dt} &= f_{\mathrm{fast}}\frac{19.0}{60.0} r_{Ll}(t)(0.5 + f_{\mathrm{Lep}+}) f_{\mathrm{NEFApI}}\left(\frac{1.4F^2}{F^2 + F_0^2} + 0.3\right)\\ &+ 0.22 \times 0.23 \times \mathrm{TGin}\\ &+ 0.25 \times \mathrm{TGin} + f_{\mathrm{fed}}\mathrm{HDNL} f_{\mathrm{HDNLML}} f_{\mathrm{HDNLI}}\\ &- f_{\mathrm{fast}}(1.5 - f_{\mathrm{Lep}+}) r_{\mathrm{VLDLTGpfast}} f_{\mathrm{VLDLTGI}} \times \frac{\mathrm{HLipid}}{\mathrm{HLipid}_0}\\ &- f_{\mathrm{fed}}(1.5 - f_{\mathrm{Lep}+}) r_{\mathrm{VLDLTGpfed}} f_{\mathrm{VLDLTGI}} \times \frac{\mathrm{HLipid}}{\mathrm{HLipid}_0}\\ &- f_{\mathrm{fast}} r_{Lox}(t)(2 f_{\mathrm{Lep}+})\tilde{g}(t)(1.5 \times r_{\mathrm{VLDLTGpfast}})\frac{\mathrm{HLipid}}{\mathrm{HLipid}_0}\\ &- f_{\mathrm{fed}} r_{Lox}(t)(2 f_{\mathrm{Lep}+})\tilde{g}(t)(1.5 \times r_{\mathrm{VLDLTGpfed}})\frac{\mathrm{HLipid}}{\mathrm{HLipid}_0}. \end{aligned} \quad (30)$$

The factors multiplying the four positive contributions represent plasma NEFA, spillover NEFA, chylomicron remnant TG and HDNL, respectively. With respect to losses, the first two terms model secretion and the last two terms model $\beta$-oxidation (fatty acid oxidation). Integrating $r_{\mathrm{VLDLTGpfast}} f_{\mathrm{VLDLTGI}}$ over 12 hours yields 12 g TG, at reference parameters. The fed contribution adds another 8 g. It is assumed that losses due to $\beta$-oxidation occur 50% faster than losses to VLDL-TG secretion at reference parameters (to balance the input and output, see Appendix D). Leptin inhibits VLDL-TG secretion [67,68] and stimulates $\beta$-oxidation [68]. Losses are scaled according to HLipid. The scaling term $r_{Lox}$ appears in the rate of change of fat mass, hepatic and muscle lipids. It is assumed that any scaling of the lipid oxidation rate due to CHO intake occurs at roughly the same rate in all tissues, with the exception that this carbohydrate dependence is enhanced in the liver [69].

### 3.14. The rate of change of muscle lipids

The rate of change of muscle lipids was modelled by

$$\begin{aligned}\frac{d\text{MLipid}}{dt} &= 0.07\times\text{TGin}\\ &+ 0.5f_{\text{fast}}(k_{\text{VLDLTGpfast}}k_{\text{CHO}}\text{VLDLTGpfast})\\ &+ 0.5f_{\text{fed}}(k_{\text{VLDLTGpfed}}k_{\text{CHO}}(1.2\times\text{VLDLTGpfast}))\\ &+ 0.6975\times 0.23\times\text{TGin}\\ &+ f_{\text{fast}}\frac{29.0}{60.0}r_{Ll}(t)(0.5+f_{\text{Lep+}})f_{\text{NEFApI}}\left(\frac{1.4F^2}{F^2+F_0^2}+0.3\right)\\ &- r_{Lox}(t)\left(f_{\text{fed}}\frac{0.92}{2.15}+f_{\text{fast}}\frac{1.23}{2.15}\right)\times(0.5+f_{\text{Lep+}})\frac{\ln(2)}{h_{\text{MLipid}}}\text{MLipid}.\end{aligned} \tag{31}$$

The first term models the arrival of CM-TG (in the fed state) and scales with TGin. The second and third terms, as for the change in fat mass equation, model a delivery of half of the circulating VLDL-TG to skeletal muscle tissue, 10 g/d when using reference parameters. The fourth term represents spillover NEFA delivery, 16 g/d when using reference parameters. The fifth term represents the delivery of NEFA from the adipose tissue (a fraction of the rate of lipolysis). The last term models losses due to $\beta$-oxidation (lipid oxidation) as a decay term. Oxidation is assumed to be proportional to the mass of skeletal muscle cells, but altered by diet and stimulated by leptin [56,68,70]. Fed and fasting rates of lipid oxidation were partitioned according to published rates ([30, Table 1]). The half-life of muscle lipid was estimated by assuming a reference mass of 300 g per 36 dl [35], i.e. 8333 mg/dl, and a rate of oxidation of 62 g TG per day. Assuming the rate equals the concentration times a decay constant, the half-life of muscle lipids was estimated to be approximately 40 h. Skeletal muscle DNL has been omitted as the contribution to MLipid is small [71].

### 3.15. The rate of change of pancreatic lipids

The rate of change of pancreatic lipids was modelled as a scaled version of the rate of change of muscle lipids, for positive terms, in the absence of evidence to the contrary, based on relative masses, plus pancreatic DNL (PDNL) and lipid oxidation, setting

$$\begin{aligned}\frac{d\text{PLipid}}{dt} &= \frac{1.5}{1000\times 0.5\times\text{LBM}}\Bigg(0.07\times\text{TGin}\\ &+ 0.5f_{\text{fast}}(k_{\text{VLDLTGpfast}}k_{\text{CHO}}\text{VLDLTGpfast})\\ &+ 0.5f_{\text{fed}}(k_{\text{VLDLTGpfed}}k_{\text{CHO}}\times(1.2\times\text{VLDLTGpfast}))\\ &+ 0.6975\times 0.23\times\text{TGin}\\ &+ f_{\text{fast}}\frac{29.0}{60.0}r_{Ll}(t)(0.5+f_{\text{Lep+}})f_{\text{NEFApI}}\left(\frac{1.4F^2}{F^2+F_0^2}+0.3\right)\Bigg)\\ &+ f_{\text{fed}}\text{PDNL}\\ &- r_{Lox}(t)\left(f_{\text{fed}}\frac{0.92}{2.15}+f_{\text{fast}}\frac{1.23}{2.15}\right)\times(0.5+f_{\text{Lep+}})\frac{\ln(2)}{h_{\text{PLipid}}}\text{PLipid}.\end{aligned} \tag{32}$$

It was assumed that the half-life of lipids in the pancreas $h_{\text{PLipid}} = h_{\text{MLipid}}$, that muscle mass is approximately half of LBM, that a pancreas weighs 1.5 g and that

$$\text{PDNL} = r_{\text{PDNL}}\left(\frac{G^2}{G_0^2+G^2}+0.5\right)\left(\frac{ACS_I f_{ACS_I}\tilde{g}(t)I}{I_0}\right)\left(\frac{L_0^2}{L_0^2+(S_L f_{S_L}\tilde{g}(t)L)^2}+0.5\right) \tag{33}$$

models glucose-induced lipogenesis in the pancreas [72], with stimulation by insulin and inhibition by leptin. The rate $r_{\text{PDNL}} = 0.2r_{\text{HDNL}}\times 1.5/1800$ is modelled on $r_{\text{HDNL}}$, scaled according to organ weights and further scaled to take account of low PDNL in healthy individuals [72], and to yield sensible values of $G$ based on the data in [51], on higher carbohydrate diets.

**Table 4**
Steady state (SS) and initial variable values by diet.

| Variable | HCLF SS | MCMF SS | LCHF SS | HCMHF SS | LE SS | LE initial |
|---|---|---|---|---|---|---|
| $G$ (mg/dl) | 93.6 | 85.0 | 81.4 | 224 | 72.2 | 164 |
| $I$ (ng/ml) | 0.424 | 0.308 | 0.234 | 0.454 | 0.286 | 0.501 |
| $\beta$-cell mass (mg) | 1983 | 1795 | 1508 | 1051 | 1414 | 1459 |
| $L$ (ng/ml) | 7.85 | 7.42 | 6.20 | 20.5 | 1.06 | 20.6 |
| $F$ (kg) | 13.8 | 13.9 | 12.0 | 45.4 | 1.70 | 43.7 |
| $Gg$ (pg/ml) | 87.6 | 78.0 | 76.0 | 107 | 69.6 | 98.8 |
| NEFA (mg TG/dl) | 9.24 | 13.8 | 16.5 | 22.8 | 2.52 | 22.1 |
| HLipid (g TG/dl) | 1.41 | 1.50 | 1.36 | 3.15 | 0.434 | 3.19 |
| MLipid (g TG/dl) | 9.98 | 8.72 | 7.76 | 22.0 | 2.28 | 21.3 |
| VLDL-TG (mg TG/dl) | 92.2 | 94.2 | 83.5 | 209 | 35.6 | 203 |
| PLipid (mg TG/dl) | 0.566 | 0.457 | 0.396 | 1.14 | 0.146 | 1.12 |

### 3.16. The rate of change of fasting plasma VLDL-TG

The rate of change of fasting plasma VLDL-TG (VLDLTGpfast) is modelled as

$$\begin{aligned}\frac{d\text{VLDLTGpfast}}{dt} &= f_{\text{fast}}\Bigg(r_{\text{VLDLTGpfast}}f_{\text{VLDLTGI}}\times(1.5-f_{\text{Lep+}})\frac{\text{HLipid}}{\text{HLipid}_0}\\ &- (k_{\text{VLDLTGpfast}}k_{\text{CHO}}\text{VLDLTGpfast})\Bigg).\end{aligned} \tag{34}$$

It was assumed that the rate of appearance of VLDL-TG from the liver is inhibited by insulin and leptin, and increased in proportion to HLipid, and that hepatic insulin resistance increases the rate of appearance. See Section 3.11, Section 3.13 and Appendix D. Initially, it was assumed that a HC diet decreases the rate of clearance. However, the term $k_{\text{CHO}} = 1.1$ in this study, set to model the baseline values of VLDL-TG seen in the DiRECT patients.

### 3.17. Steady state behaviour

For the determination of steady states, an autonomous system with eleven variables is assumed, replacing the transient function of time $\tilde{g}(t)$ by $g(y_{\text{CHO}})$ (see Appendix B). At the reference parameters given in Table 2, the dynamical system has one physiological stable steady state, given by the MCMF steady state variable values in Table 4, and one pathological unstable steady state with very high $G$, high $Gg$, $I = 0$, physiological values of other biomarkers and $\beta = 0$.

At the physiological stable steady state, the eleven-dimensional Jacobian matrix has eleven eigenvalues with negative real parts. At the unstable steady state (with $\beta = 0$ and hence $I = 0$), the Jacobian matrix has ten eigenvalues with negative real parts and one positive real eigenvalue. This unstable steady state lies in a stable manifold, which is locally a ten-dimensional manifold, defined by $\beta = 0$.

The current long-term model was based on a model of $G$, $I$ and $\beta$, by Topp et al. [22], in which the rate of change of $\beta$ is a quadratic equation in $G$. This results in a limit point at physiological values of biomarkers. However, when lipids are introduced to the model, it is no longer necessary to make glucotoxicity a proxy for lipotoxicity. Updating the rate of change of $\beta$-cell mass to depend upon $G$ and PLipid results in the removal of the quadratic equation in $G$ from the rate of change of $\beta$-cell mass in the original model by Topp et al. [22]. This in turn results in shifts in dynamics, the loss of a limit point at physiological values of biomarkers. This allows the plotting of realistic time courses corresponding to various diets, without a sudden loss of stability at physiological parameters.

In summary, given parameters with physiological values, the model predicts

1. one physiological stable steady state (with $\beta$-cell mass $\beta > 0$),
2. one pathological unstable steady state (with $\beta = 0$, that is, type 1 diabetes),
3. a stable manifold defined locally by $\beta = 0$

Practically, given a diet and a starting point in phase space, a trajectory will lead to a steady state with positive $\beta$-cell mass unless complete $\beta$-cell failure occurs (type 1 diabetes).

## 4. Method

### 4.1. Trajectories simulated

In order to simulate a path to overweight type 2 diabetes followed by weight loss and remission and, in some cases, subsequent relapse, the general steps given below were followed, producing three sets of simulations. A remission trajectory is a trajectory with a steady state value for $G < 126$ mg/dl.

1. (a) Start at the MCMF steady state (SS). See Table 4.
   (b) Follow the (red) HCMHF trajectory for six years.
   (c) Leave on a (black) low-energy (LE) remission trajectory (the LE diet).
   (d) Follow the LE diet short-term.
   (e) Leave at a chosen fat mass, denoted $F_c$, once $G$, $I$ and VLDL-TG have settled to healthy values for a few weeks or months. Assume that $F_c \geq F_{\text{MCMFSS}}$, where the latter denotes the steady state value of fat mass on the MCMF diet.
   (f) Stay on a diet which approximately maintains fat mass. The diets simulated have steady state fat masses matching the fat mass at which the LE diet is abandoned, except for the moderate-energy diets yielding the trajectories from $F = 15$ kg, on which fat mass falls slightly. See Figs. 3–7. A note on how the diets were determined is given in Section 4.2.
   (g) Follow the trajectory towards steady state.
2. (a) Start at the MCMF steady state (SS).
   (b) Follow the HCMHF trajectory for six years.
   (c) Leave on a low-energy remission trajectory (the LE diet).
   (d) Leave the LE diet at a chosen fat mass, $F_c \geq F_{\text{MCMFSS}}$.
   (e) Stay on a ME diet, for example, the (green) LCHF, (orange) MCMF or (blue) HCLF diet. These diets differ in lipid to carbohydrate ratios. See Fig. 8.
   (f) Follow the trajectory towards steady state.
3. (a) Start at the MCMF steady state (SS).
   (b) Follow the HCMHF trajectory for six years.
   (c) Leave on a ME diet, for example, the (green) LCHF, (orange) MCMF or (blue) HCLF diet. These diet differ in lipid to carbohydrate ratios. See Fig. 9.
   (d) Follow the trajectory towards steady state.

### 4.2. Diets which maintain fat mass

The diets that approximately maintain fat mass were defined in one of two ways, described below. All these diets were assumed to contain 100 g protein. Carbohydrate and lipid content varied.

1. Diets were defined as multiples of the HCLF, the MCMF or the LCHF diet, with respect to the lipid and carbohydrate energy contributions. For example, all multiples of the HCLF diet have the same lipid to carbohydrate energy ratio, namely $(51.78 \times 9)/(400 \times 4) = 0.291$, assuming 9 kcal per gram of lipid and 4 kcal per gram of carbohydrate. The ratio for the MCMF diet is one and the ratio for the LCHF diet is $(176.22 \times 9)/(120 \times 4) = 3.30$. The multiple is denoted $x$.
   (a) Multiples of the LCHF diet: $x(176.22)$ g/d lipid plus $x(120)$ g/d carbohydrate plus 100 g/d protein. See Fig. 3.
   (b) Multiples of the MCMF diet: $x(114)$ g/d lipid plus $x(260)$ g/d carbohydrate plus 100 g/d protein. See Fig. 4.
   (c) Multiples of the HCLF diet: $x(51.78)$ g/d lipid plus $x(400)$ g/d carbohydrate plus 100 g/d protein. See Fig. 5.

   The mapping of $x \geq 1$ to the steady state fat mass of the diet so defined is an increasing function for the LCHF and MCMF multiples and the lower HCLF multiples. For higher multiples of the HCLF diet this is not so since, in the model, very high carbohydrate consumption results in very low insulin sensitivities, high $G$ and fat mass settling at approximately 27 kg for multiples near 1.25. However, in all examples investigated, the mapping of $x \geq 1$ to the steady state fasting plasma glucose concentration of the diet so defined is an increasing function.
2. Diets were defined as linear interpolations between the HCMHF diet and a diet of moderate energy, with respect to the carbohydrate and lipid energy contributions.
   (a) Linear interpolation from the HCMHF diet to the LCHF diet: carbohydrate content $400 + x(120 - 400)$ g/d and lipid content $145.11 + x(176.22 - 145.11)$ g/d plus 100 g protein, where $0 \leq x \leq 1$. See Fig. 6.
   (b) Linear interpolation from the HCMHF diet to the MCMF diet: carbohydrate content $400 + x(260 - 400)$ g/d and lipid content $145.11 + x(114 - 145.11)$ g/d plus 100 g protein, where $0 \leq x \leq 1$, not shown.
   (c) Linear interpolation from the HCMHF diet to the HCLF diet: carbohydrate content 400 g/d and lipid content $145.11 + x(51.78 - 145.11)$ g/d plus 100 g protein, where $0 \leq x \leq 1$. See Fig. 7.

   The mapping of $x$ to the steady state fat mass of the diet so defined is a decreasing function, in all three cases.

## 5. Results

### 5.1. Interpreting the figures

Time is marked in the following way in Figs. 3–9: one diamond per week for the first 24 weeks and one hexagram per 6 months, for up to 10 years. Large black pentagrams mark trajectory starting points. Coloured hexagrams mark steady states (in practice, simulation to 100 years).

The trajectories in Figs. 3–7 should be interpreted in the following way. Start at the MCMF steady state, marked by a black pentagram. Follow the red HCMHF trajectory for six years. From this point, marked by a black pentagram, leave on the black LE 850 kcal/d remission trajectory. Points at which the LE trajectory are subsequently abandoned are marked by black pentagrams. These correspond to 6, 9, 12, 16 and 21 weeks on the LE diet, roughly corresponding to decrements of 5 kg in $F$. The LE trajectory is abandoned for a trajectory that maintains fat mass assuming a multiple of the LCHF diet, or a multiple of the MCMF diet, or a multiple of the HCLF diet, or a diet found by linear interpolation from the HCMHF diet to the LCHF diet, or a diet found by linear interpolation from the HCMHF diet to the HCLF diet; in Figs. 3–7, respectively. Figs. 8 and Fig. 9 should be interpreted in a similar way. In the former, the graph represents leaving on the LCHF, MCMF and HCLF diets after 12 weeks on the LE diet. In the latter, the graph represents leaving on the LCHF, MCMF and HCLF diets after 6 years on the HCMHF diet. Fig. 10 shows the HGP versus $I$ projections relating to Figs. 3–9, respectively. In summary, a variety of paths from health to disease, followed by remission and possible relapse are presented (see Fig. 11).

### 5.2. The HCMFH trajectory to overweight type 2 diabetes

All the scenarios investigated begin with a HCMHF trajectory to overweight type 2 diabetes, plotted in red in Figs. 3–9, starting from a healthy MCMF steady state. The first twenty four weeks of the trajectories are marked by diamonds, one per week. Over the first few

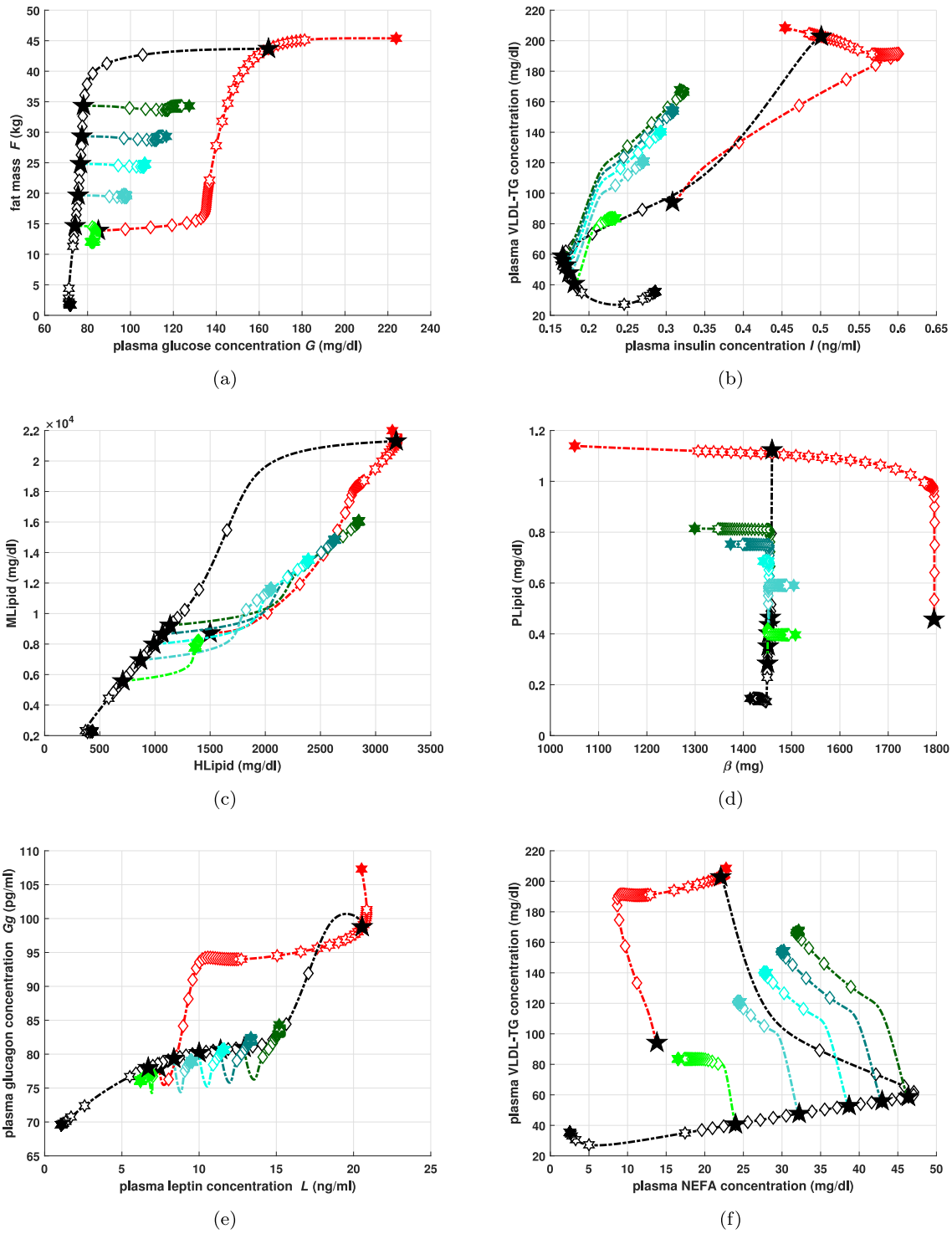



**Fig. 3.** Start at the MCMF steady state, marked by a black pentagram. Follow the red HCMHF trajectory. Time is marked in the following way: one diamond per week for the first twenty four weeks and one hexagram per six months, for up to ten years. Steady state is marked with a coloured hexagram. After six years on the red HCMHF trajectory, leave (at a black pentagram) on the black LE 850 kcal/d remission trajectory, plot to steady state, marking points at which the trajectory is left by black pentagrams. Leave the black remission trajectory on trajectories which maintain fat mass. These trajectories represent multiples of the LCHF diet at (a) $F = 34.3$ kg (after 6 weeks, dark green, multiple $x = 1.758$), (b) $F = 29.3$ kg (after 9 weeks, teal, $x = 1.67$), (c) $F = 24.8$ kg (after 12 weeks, cyan, $x = 1.568$), (d) $F = 19.7$ kg (after 16 weeks, turquoise, $x = 1.408$) and (e) $F = 14.7$ kg (after 21 weeks, green, $x = 1.0$). See Section 4.2. All trajectories are plotted to steady state.

weeks, muscle, hepatic and pancreatic lipids rise as hepatic insulin sensitivity falls, the latter causing HGP to rise. See Fig. 10. Fasting plasma concentrations of VLDL-TG, glucose, insulin and glucagon rise. NEFA falls over the first few weeks as high carbohydrate intake slows lipolysis. The $\beta$-cell mass is almost constant. Fat mass rises slowly.

As lipid oxidation and lipolysis slow down with increased carbohydrate intake, all lipids, and fasting plasma concentrations of glucose, leptin and glucagon continue to rise slowly towards steady state values, while (differentiated) $\beta$-cell mass and insulin begin to fall. Six-monthly intervals on the trajectories are marked by hexagrams. The trajectory is abandoned at six years, the point on the trajectory marked by a large

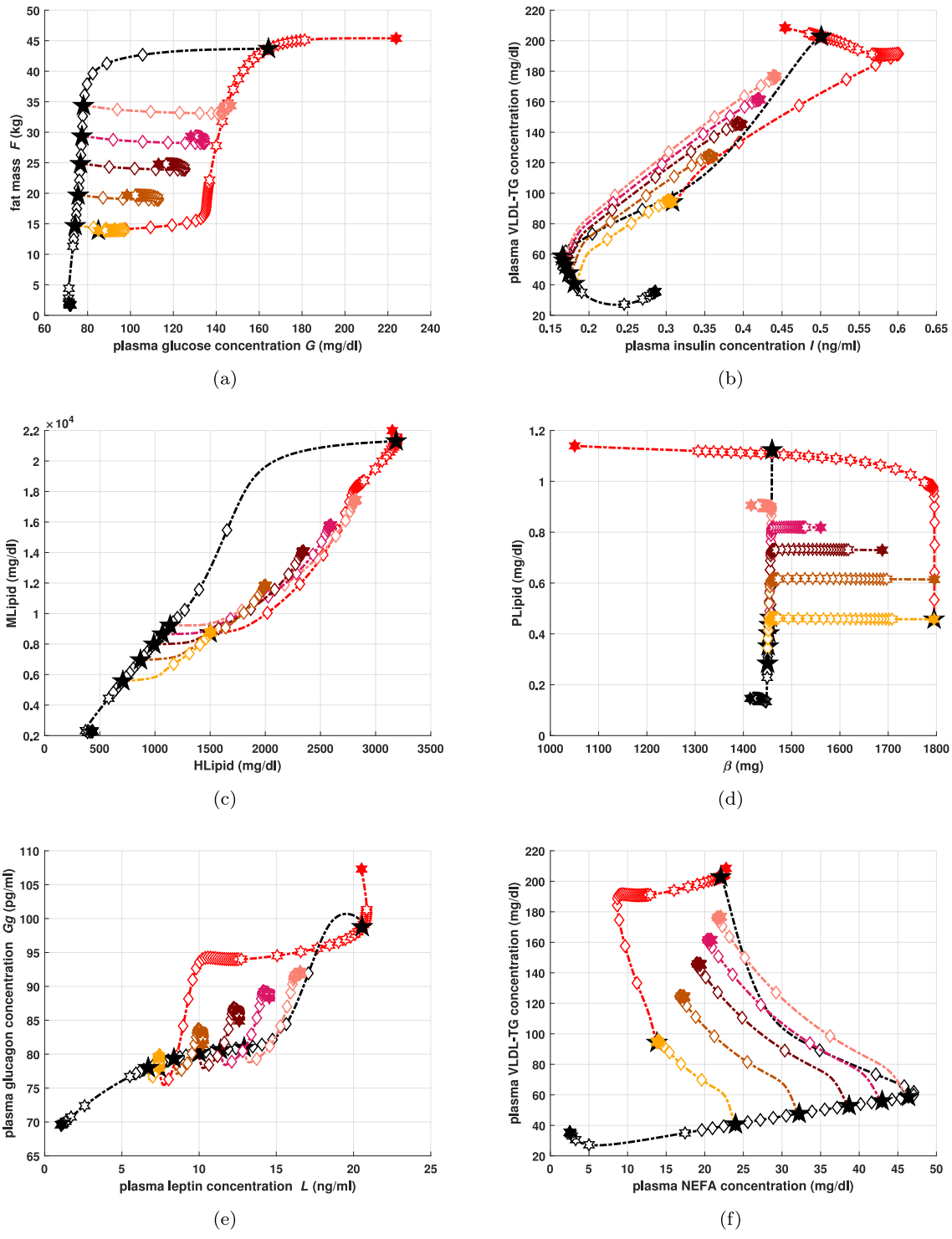



**Fig. 4.** This figure is to be interpreted in the same way as Fig. 3. The trajectories at which the LE trajectory is abandoned maintain fat mass. They represent multiples of the MCMF diet at (a) $F = 34.3$ kg (after 6 weeks, salmon, $x = 1.369$), (b) $F = 29.3$ kg (after 9 weeks, crimson, $x = 1.32$), (c) $F = 24.8$ kg (after 12 weeks, maroon, $x = 1.262$), (d) $F = 19.7$ kg (after 16 weeks, brown, $x = 1.17$) and (e) $F = 14.7$ kg (after 21 weeks, orange, $x = 1.0$). See Section 4.2.

black pentagram. Variable values at this point are consistent with mean baseline values from the DiRECT trial, representing overweight type 2 diabetes.

### 5.3. The short-term low-energy diet

Simulations representing an approach to fat mass loss and remission from type 2 diabetes that is based on a low-energy diet followed a diet which maintains fat mass are plotted in Figs. 3–7. This approach is typical of many clinical trials and advice from health professionals. Values of $HbA_{1c}$ are not simulated. Instead, $G < 126$ mg/dl is used to define remission. It is assumed that values of $G < 126$ mg/dl maintained for the previous three months should correspond to healthy $HbA_{1c}$ measurements.

The (black) low-energy diet trajectory starts at the marker representing six years on the HCMHF diet trajectory, at a state which

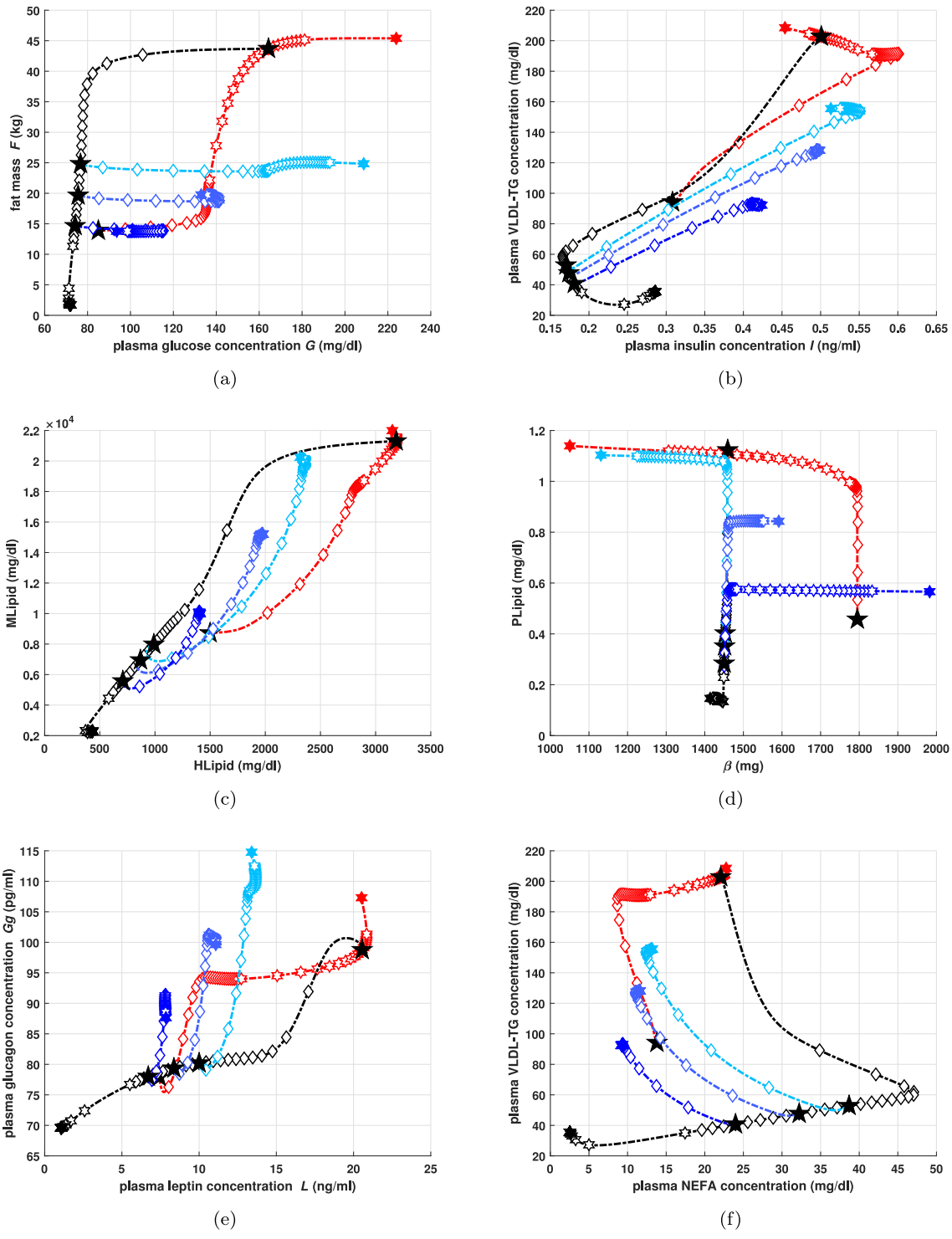



**Fig. 5.** This figure is to be interpreted in the same way as Fig. 3. The trajectories at which the LE trajectory is abandoned maintain fat mass. They represent multiples of the HCLF diet at (a) $F = 24.8$ kg (after 12 weeks, light blue, $x = 1.173$), (b) $F = 19.7$ kg (after 16 weeks, mid blue, $x = 1.113$) and (c) $F = 14.7$ kg (after 21 weeks, blue, $x = 1.0$). See Section 4.2.

represents overweight type 2 diabetes. See Table 4. On the LE trajectory, HLipid falls to the healthy MCMF steady state value in one to two weeks and PLipid falls to the healthy MCMF steady state value in six to nine weeks. As a result, hepatic insulin sensitivity is predicted to normalise in the first two weeks, before the slow process of $\beta$-cell redifferentiation is noticeable. Fasting plasma variables VLDL-TG, $G$ and $I$ fall rapidly, in the first few weeks, approaching their LE diet steady state values in this period. Lipids and leptin are very low at steady state on the LE diet. It is not expected that the LE diet would be followed to steady state, only for a few weeks or months, and no longer than it takes for fat mass to reach a value close to the MCMF steady state value. In the simulations shown, this is six months. On the LE trajectory, remission is achieved in one week and lasts until the diet is abandoned. Although the LE diet trajectory is a remission trajectory, it is unsustainable (too low in energy to follow long-term).

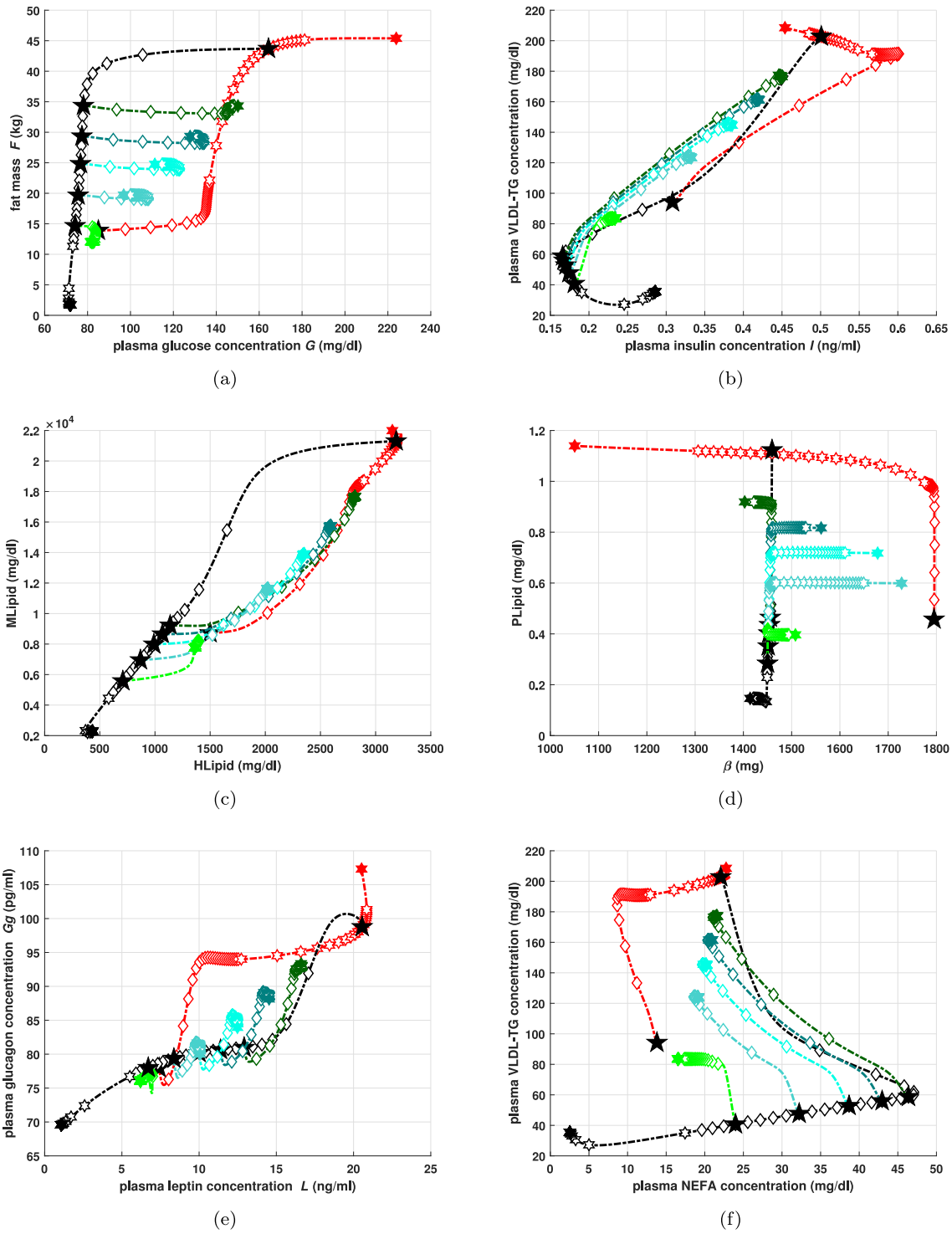



**Fig. 6.** This figure is to be interpreted in the same way as Fig. 3. The trajectories at which the LE trajectory is abandoned maintain fat mass. They represent diets found by linear interpolation from the HCMHF diet to the LCHF diet at (a) $F = 34.3$ kg (after 6 weeks, dark green, $x = 0.127$), (b) $F = 29.3$ kg (after 9 weeks, teal, $x = 0.208$), ((c) $F = 24.8$ kg (after 12 weeks, cyan, $x = 0.308$), (d) $F = 19.7$ kg (after 16 weeks, turquoise, $x = 0.472$) and e) $F = 14.7$ kg (after 21 weeks, green, $x = 1.0$). See Section 4.2.

### 5.4. Fast, slow and very slow variables

It is thought that excess fat in the liver and pancreas contribute to a loss of hepatic insulin sensitivity and to a loss of $\beta$-cell function, respectively. Losing this extra lipid can reverse these changes and enable remission. This is the twin cycle hypothesis. Patients who have had type 2 diabetes for shorter times are likely to have suffered less $\beta$-cell dedifferentiation. The processes of $\beta$-cell dedifferentiation and redifferentiation are very slow (based on past estimates of birth and death rates [28] and more recent research [11]), slower to steady state than fat mass. Simulations are consistent with this scenario.

Both hepatic and pancreatic lipids are predicted to increase rapidly and concurrently on a high energy diet, such as the HCMHF diet. Both lipids are predicted to return to lower (healthier) values rapidly and concurrently on a low-energy or moderate-energy diet, over a few weeks, the timing depending on the diet. Changes in hepatic and

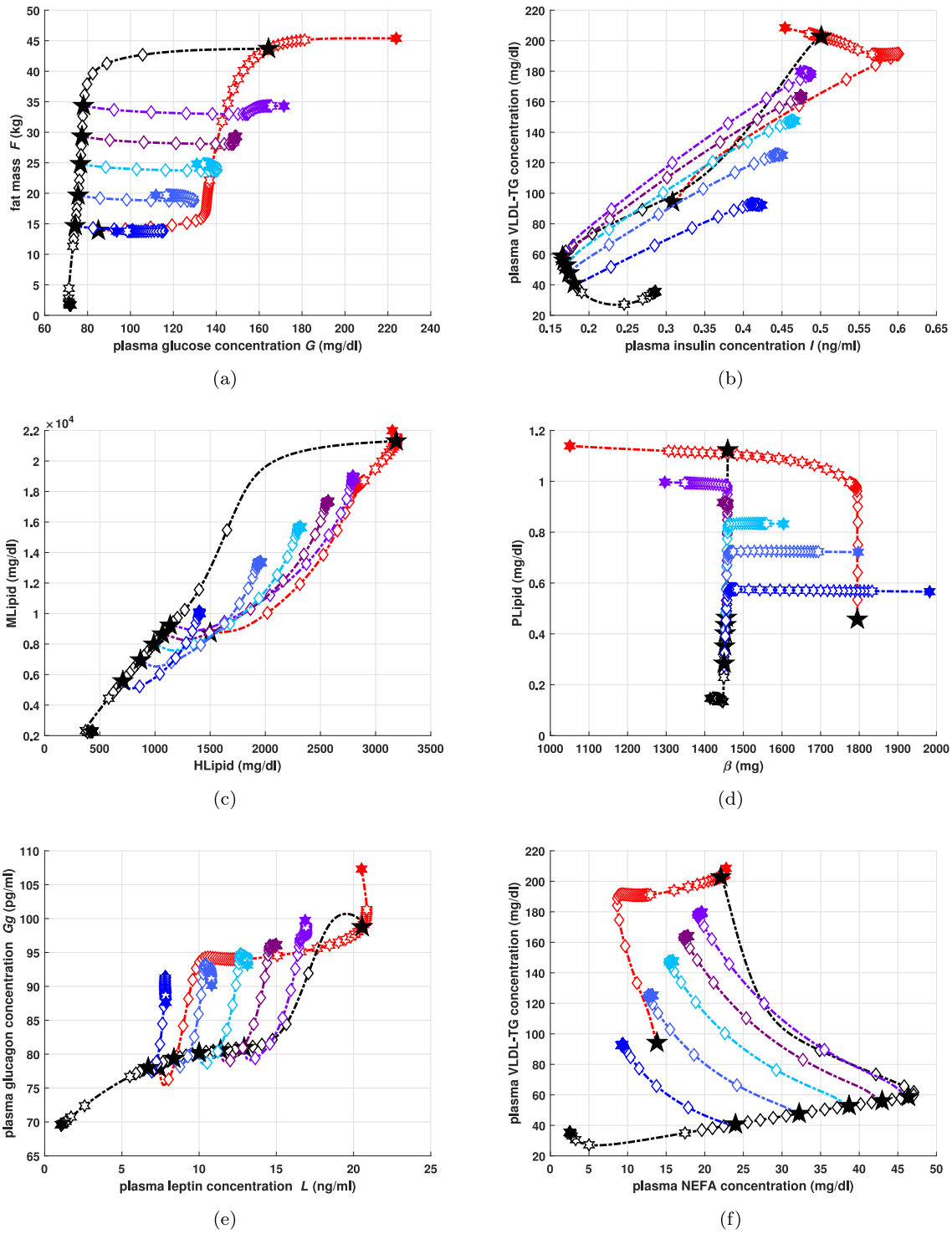



**Fig. 7.** This figure is to be interpreted in the same way as Fig. 3. The trajectories at which the LE trajectory is abandoned maintain fat mass. They represent diets found by linear interpolation from the HCMHF diet to the HCLF diet and so differ only in lipid content. Leave at (a) $F = 34.3$ kg (after 6 weeks, dark purple, $x = 0.244$), (b) $F = 29.3$ kg (after 9 weeks, light purple, $x = 0.378$), (c) $F = 24.8$ kg (after 12 weeks, sky blue, $x = 0.52$), (d) $F = 19.7$ kg (after 16 weeks, darker sky blue, $x = 0.715$) and (e) $F = 14.7$ kg (after 21 weeks, blue, $x = 1.0$). See Section 4.2.

pancreatic lipids lead to changes in plasma glucose levels, on different time scales, hepatic insulin sensitivity and HGP changing much faster (with hepatic lipid, see Fig. 10) than $\beta$-cell function (with pancreatic lipid). In Figs. 3(a)–9(a), the effects on $G$ of increasing HLipid and PLipid may be seen on the HCMHF weight gain trajectory to type 2 diabetes. Over the first few weeks, HLipid increases rapidly and, as a result, hepatic insulin sensitivity rapidly decreases, HGP rapidly increases and $G$ rapidly increases, matching the initial (lower) part of the S-shaped curve in the $(G, F)$ projections. After six to nine weeks, gains in PLipid are slowing down and loss of $\beta$-cell function begins, mainly responsible for the slower increases in $G$ towards steady state on the remainder of the S-shaped curve. On the LE trajectory, $G$ normalises within one week and deficiencies in $\beta$-cell function (represented by lower $\beta$-cell mass in the model) are compensated by an increase in

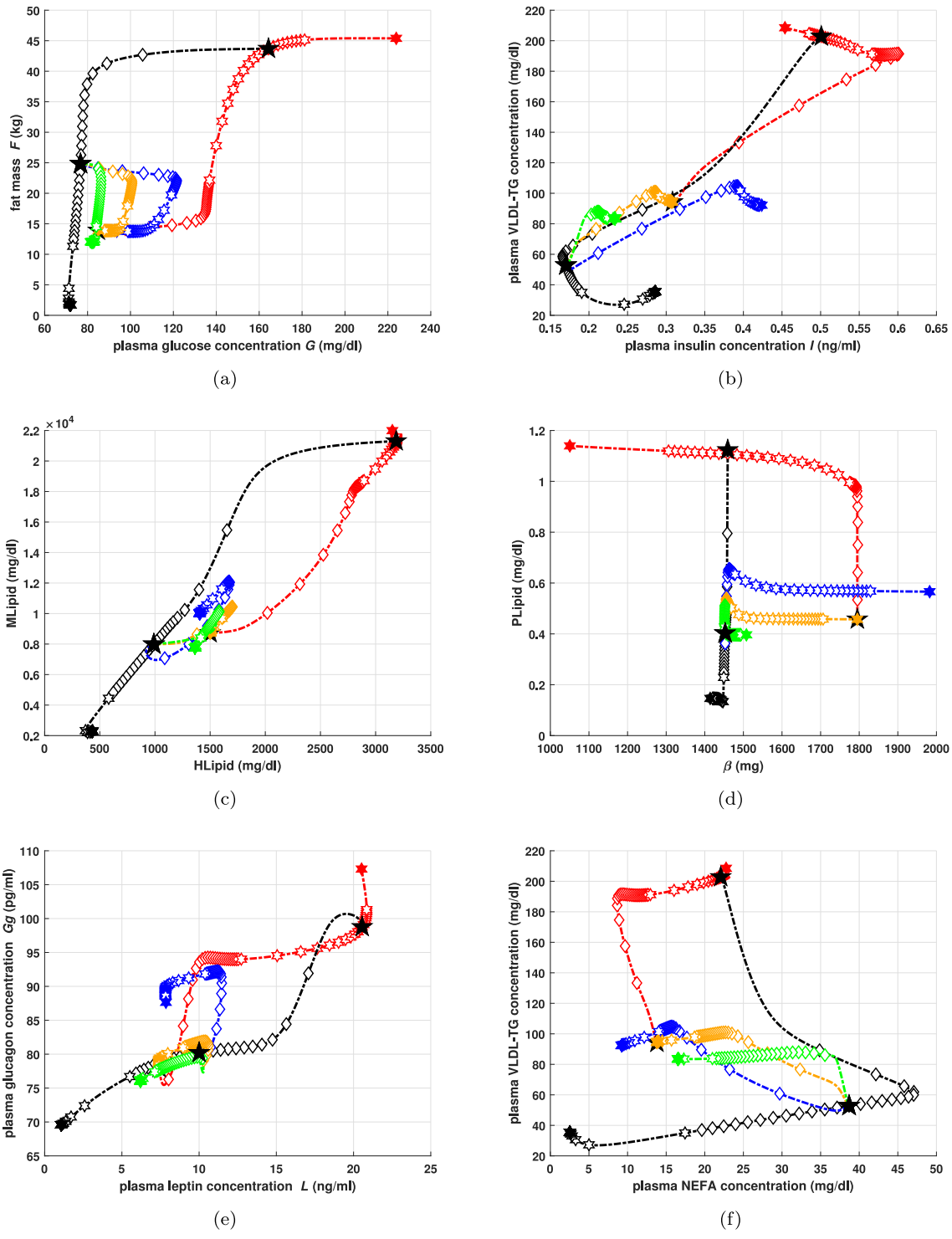



**Fig. 8.** Start at the MCMF steady state, marked by a black pentagram covered by an orange hexagram. Time intervals and steady states are marked as in Fig. 3. After 6 years on the HCMHF trajectory, leave, at a black pentagram, on the black LE 850 kcal/d remission trajectory. Leave the LE trajectory at $F = 24.8$ kg (after 12 weeks) on (a) the green LCHF trajectory, (b) the orange MCMF trajectory or (c) the blue HCLF trajectory. Follow the chosen ME diet trajectory to steady state.

hepatic insulin sensitivity. Recall that it is assumed that parameters and rates are able to return to normal in those who have had type 2 diabetes for a short duration. On the unsustainable LE remission trajectory, $\beta$-cell redifferentiation causes already healthy values of $G$ to fall slightly and very slowly. Hence, $G$ has a fast component caused by changes in HLipid and a very slow component caused by changes in PLipid. Measuring for only two years from a change in diet, the very slow component could be missed. Similarly, $I$ has a fast component and a very slow component. The very slow component of $G$ is much more noticeable in the graphs than the very slow component of $I$. This is because a loss of insulin sensitivity alone increases $I$ and $G$, whereas a loss of $\beta$-cell function alone decreases $I$ while increasing $G$. In practice, a loss of $\beta$-cell function usually occurs with a loss of hepatic insulin sensitivity (too much lipid in both liver and pancreas). Opposing influences make changes harder to spot. Changes in fat mass happen slowly. In the model, it is assumed that, in the liver, insulin inhibits

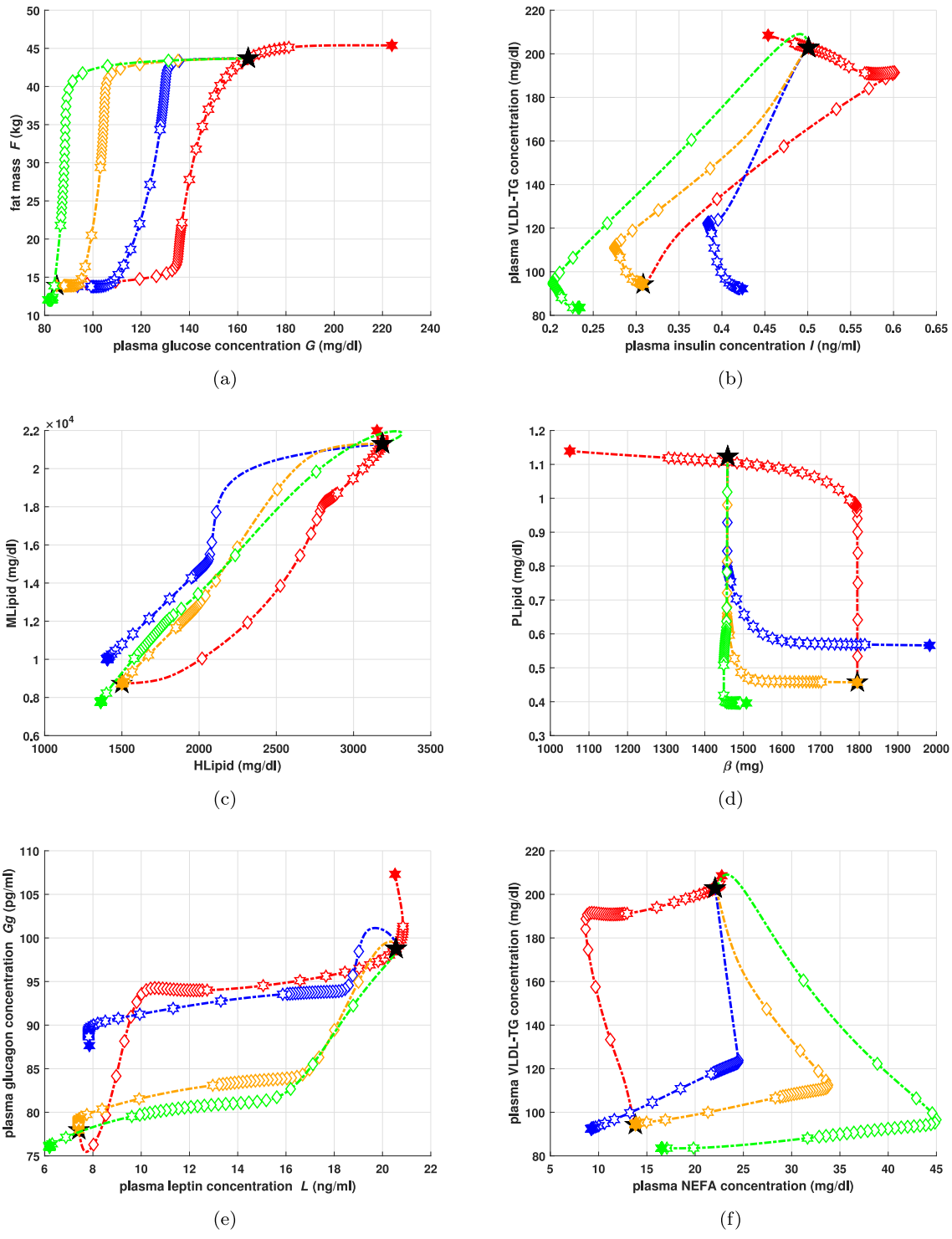
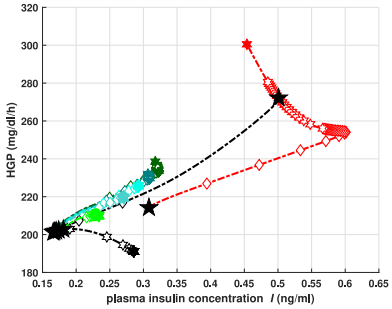



**Fig. 9.** Start at the MCMF steady state, marked by a black pentagram covered by an orange hexagram. Time intervals and steady states are marked as in Fig. 3. After six years on the red HCMHF trajectory leave, at a black pentagram, on (a) the green LCHF trajectory, (b) the orange MCMF trajectory or (c) the blue HCLF trajectory. Follow the chosen ME diet trajectory to steady state.

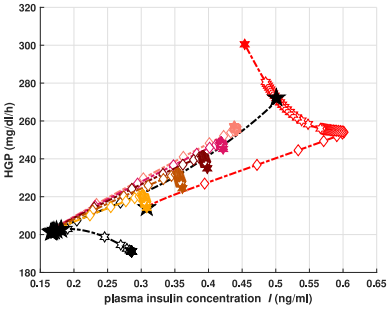
VLDL-TG secretion. As hepatic insulin sensitivity decreases with hepatic lipid, this inhibition becomes less effective. The problem with relying on a subset of variables (such as $F$, $G$, $I$ and VLDL-TG) to make a decision concerning a change of trajectory is that some variables are faster than others to approach steady state values. The relative speeds depend upon the underlying biology. In the short term, slow fat mass loss is generally a very poor measure of the success of a diet.

### 5.5. A modelling view of remission followed by relapse

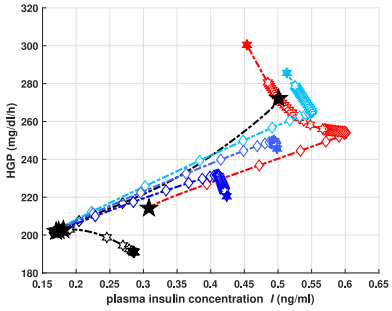
Remission followed by relapse, in a modelling sense, is equivalent to changing from a trajectory with steady state $G < 126$ mg/dl (for example, on a diet of low or moderate energy) to another trajectory with steady state $G \geq 126$ mg/dl. It is assumed that a recovery plan that begins with a change to an unsustainable LE diet will be followed by a



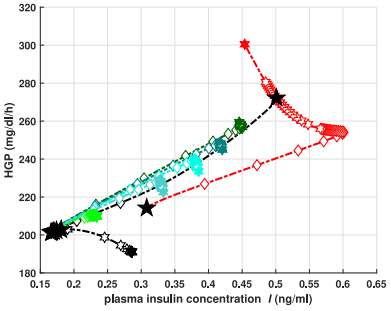

(a) Recovery: LE, multiples of LCHF



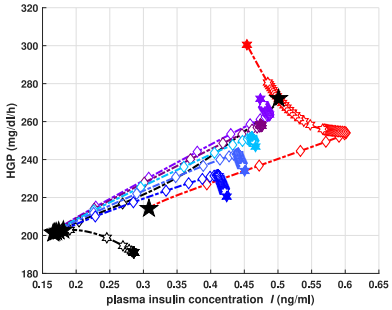

(b) Recovery: LE, multiples of MCMF



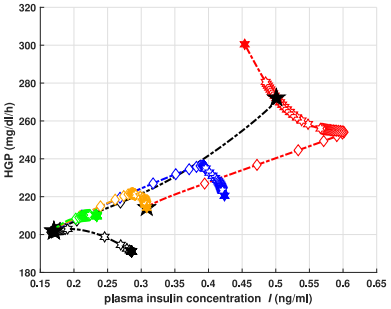

(c) Recovery: LE, multiples of HCLF



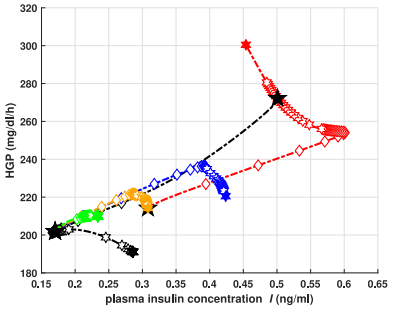

(d) Recovery: LE, linear interpolation to LCHF




(e) Recovery: LE, linear interpolation to HCLF




(f) Recovery: Low energy to moderate energy




(g) Recovery: Moderate energy

**Fig. 10.** HGP versus $I$ on trajectories, graphs (a)–(g) correspond to Figs. 3–9, respectively.

final sustainable diet after a few weeks. The steady state value of $G$ for the final diet determines the outcome, remission or relapse. Examples of final trajectories that maintain fat mass are given in Figs. 3–7, since patients are often advised to lose a certain amount of weight, and then directed to try to maintain the weight loss. For recovering patients who have had type 2 diabetes for a shorter duration, most of the changes in $G$ will be due to the fast component and values of $G$ on a trajectory will approach the steady state value within a few weeks.

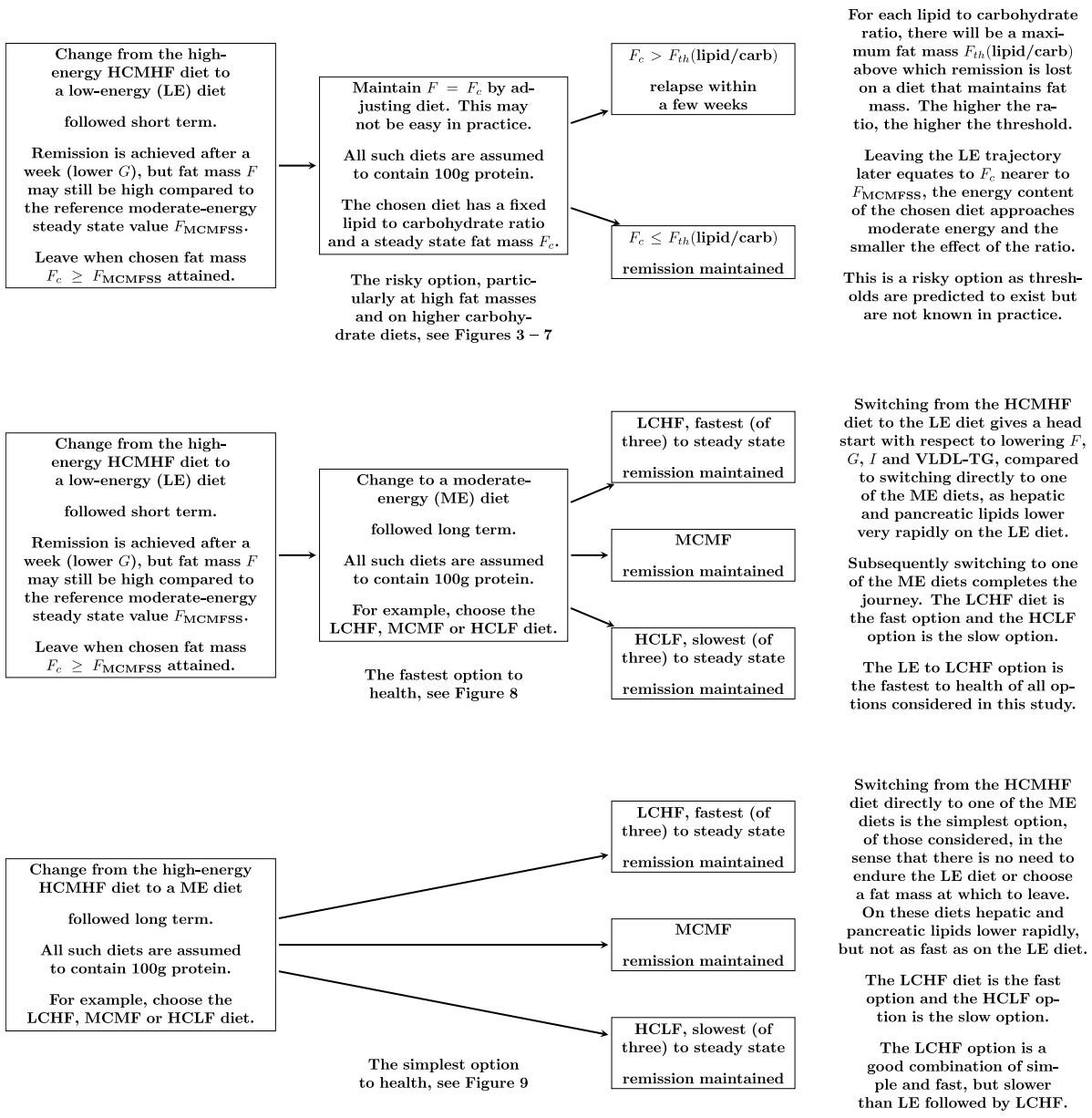



**Fig. 11.** Recovering from diet-induced type 2 diabetes: model predictions concerning remission and relapse. The relapse diets investigated are weight-maintaining diets. In general, relapse diets are not necessarily weight-maintaining diets. The outcome depends solely on the steady state value of $G$ for the final diet.

### *5.6. Leaving the low-energy diet on a trajectory that maintains fat mass, remission or relapse?*

The model predicts that leaving the low-energy diet on a trajectory that maintains fat mass will result in maintaining remission if the fat mass at which the low-energy diet is left is sufficiently low. In addition, for a given individual, the maximum value of fat mass at which the LE diet could be abandoned for a diet that maintains both fat mass and remission, depends on the lipid to carbohydrate ratio of the chosen diet. See Figs. 3–7. In the case of a diet that maintains fat mass, the higher the ratio of lipid to carbohydrate, the lower the value of $G$, at any chosen time, in all cases examined. Hence, it is predicted that, for a given energy consumption (if not too high), a patient who is prepared to follow a lower carbohydrate approach may leave at higher fat mass, whilst maintaining both fat mass and remission. For example, on a multiple of the LCHF diet, a patient could leave at $F = 25$ kg and maintain fat mass and remission, while this would not be so on a multiple of the HCLF diet. On the latter diet, maintaining $F = 25$ kg leads to a loss of remission.

The model predicts that, with respect to overweight type 2 diabetes, it is not how much weight is lost, but how close a patient can get to a healthy fat mass that matters, as well as the lipid to carbohydrate ratio of the subsequent weight-maintaining diet. This prediction is consistent with the variation in remission success reported in the DiRECT study [2]. Recall that, in this study, a healthy fat mass is considered to be one which is stable over time and concurrent with healthy values of other measures of well-being such as $G$, $I$ and VLDL-TG. This is consistent with a fat mass at which whole body lipolysis is close to the reference value. Note the $F/F_0$ terms in the equations. Reported baseline data support a choice of $F = 43$ kg at the beginning of recovery, after six years on the HCMHF diet, approximately 28 kg above the healthy values. Losing 15 kg fat mass takes the patient's fat mass to $F = 28$ kg. Leaving the low-energy diet at $F = 28$ kg and maintaining this fat mass is predicted to successfully maintain remission on a multiple of the LCHF diet, to be borderline successful

on a multiple of the MCMF diet and to fail on a multiple of the HCLF diet. See Figs. 3–5. Predictions are consistent with the conclusion based on experimental evidence from the clinical trials that patients should aim to lose at least 15 kg. The simulations correspond to a person with a lean body mass of 60 kg. For such a person, aiming for a fat mass no more than 5 to 10 kg above a typical healthy fat mass (12 to 14 kg in this study) and maintaining carbohydrate intake less than or equal to approximately 400 g/d, is predicted to result in success. For the overweight, the closer to a healthy fat mass, the smaller the effect of the lipid to carbohydrate ratio in the weight-maintaining diet.

Practical problems with this approach include maintaining the motivation to stay on a low-energy diet for a few weeks to months, guessing a suitable fat mass at which it is safe to leave the low-energy trajectory, and then maintaining this fat mass. This approach is risky, since fat mass thresholds, although predicted to exist, are not known in advance. Given a lipid to carbohydrate ratio of a proposed diet, leaving at a fat mass that is too high is predicted to result in relapse in a few days to a few weeks.

Advantages of this approach include the rapid lowering of hepatic and pancreatic lipids on the low-energy trajectory and the resulting rapid remission, although remission may be short-lived once the unsustainable LE trajectory is abandoned.

### 5.7. Leaving the low-energy diet on a more general diet trajectory, remission or relapse?

Patients may leave a low-energy diet on diets that do not maintain fat mass. In any case, it is the diet parameters and hence the steady state value of $G$ which determine the outcome, either relapse or lasting remission.

### 5.8. Leaving the low-energy diet on a moderate-energy diet trajectory

Switching from the HCMHF diet to the LE diet, before switching to a ME diet, gives a head start with respect to lowering $F$, $G$, $I$ and VLDL-TG, compared to switching directly from the HCMHF diet to one of the ME diets, as hepatic and pancreatic lipids respond very rapidly to a change of diet. The magnitude of the response is linked to the degree of change in carbohydrate content and overall energy content. Compare Figs. 8 and 9. All three moderate-energy diets have steady states with healthy variable values and hence lead to remission. The LCHF diet is the fast option, the MCMF is intermediate in speed and the HCLF option is the slow option. The LE diet followed by the LCHF diet is the fastest to health of all options considered in this study. The LE diet followed by the HCLF diet maintains the remission achieved by following the LE diet, although the change to the HCLF diet is predicted to temporarily result in pre-diabetes ($100 < G \leq 125$ mg/dl) which gradually improves. The HCLF diet shows higher $I$ and $\beta$-cell mass at steady state than the MCMF diet which in turn shows higher values than those for LCHF diet, since higher insulin secretion is needed to balance the higher glucose intake at lower insulin sensitivity. With respect to the options considered, a short-term (unsustainable) low-energy diet, followed by a long-term moderate-energy trajectory is the fastest way to health. See Fig. 8.

### 5.9. Recovery on a long-term moderate-energy diet

Switching from the HCMHF diet directly to one of the ME diets is the simplest option, of those considered, in the sense that there is no need to endure the LE diet or to choose a sensible fat mass at which to leave. Remission is predicted to be fast and durable, achieved in one week, improving over the next few weeks. On these diets, hepatic and pancreatic lipids lower rapidly, but not as fast as on the LE diet. The LCHF diet is the fast option, the MCMF diet is intermediate in speed and the HCLF diet is the slow option. The LCHF option is a good combination of simple and fast, but slower than LE diet followed by LCHF diet. A long-term moderate-energy trajectory is the simplest way to health. See Fig. 9. Practical advantages of this approach include needing to choose only one (sustainable) remission diet. The patient would be expected to stay on this diet for the long term. Fat mass loss is predicted to be slow compared to the fast components of $G$, $I$ and VLDL-TG, but to continue slowly and surely towards a healthy steady state value.

## 6. Discussion

### 6.1. Type 2 diabetes remission trials

The model takes into account the twin cycle hypothesis [16]. The Counterpoint study [15,73], reported in 2011, with 11 obese participants with type 2 diabetes, tested this hypothesis and confirmed that, for obese patients with type 2 diabetes, calorie restriction normalised liver fat content and hepatic insulin sensitivity, normalising HGP in seven days. Pancreatic fat content and first phase insulin response normalised in eight weeks. The subsequent Counterbalance study [4,16], reported in 2016, with 30 overweight or obese participants with type 2 diabetes diagnosed up to 23 years prior to the trial, showed that if weight was kept steady after rapid weight loss due to calorie restriction, then remission from type 2 diabetes was durable, for up to six months, for 13 out of 30 participants. This study also showed that reversibility was less likely for those with type 2 diabetes with a duration of at least 10 years [51]. These small studies led to the large DiRECT trial [1], reported in 2018 and 2019, with 149 participants, in which it was demonstrated that a few weeks on a very low calorie diet (VLCD) followed by weight maintenance could result in durable remission from type 2 diabetes for up to two years, for 36% of the participants. The Counterpoint VLCD had an energy content of 600 kcal/d, the Counterbalance VLCD corresponded to 624–700 kcal/d and the later DiRECT VLCD, modelled in this article, had an energy content of 850 kcal/d. In the Counterpoint, Counterbalance and DiRECT studies, the VLCD was followed for a few weeks or months, followed by a stepped reintroduction of more food, with guidelines based on maintaining weight loss, with the aim of retaining remission for responders. Similar trials have since been carried out, in different populations, for example, a Thai study [74] in which 79% of participants achieved remission at 12 weeks and 30% of participants achieved remission at 12 months; and a study done in Qatar (DIADEM-I) [75], in which 61% of intervention participants achieved remission at 12 months. All five trials have been compared in a review [6].

Other studies have shown that, for patients with type 2 diabetes, bariatric surgery initiates remission in one week [76,77], and acute weight loss together with a loss of pancreatic lipid at eight weeks after surgery [51,78]. In addition, there is evidence that pancreatic lipid is the cause of $\beta$-cell dysfunction, via *in vitro* studies on $\beta$-cells [79,80] and via observing losses in pancreatic lipid after bariatric surgery in patients with type 2 diabetes [51,78,81]. It is thought that pancreatic $\beta$-cell dedifferentiation is a mechanism for diabetic $\beta$-cell failure [17–19].

The assumption that diet-induced type 2 diabetes has developed relatively recently (over a few years) is consistent with the view that metabolic rates and hence lipid levels can return to healthy values after a change in diet. It is thought that rates and hence lipid levels may not adjust so well after prolonged type 2 diabetes since remission from type 2 diabetes is less likely after longer disease duration [51]. Remission trials are generally limited to those who have diabetes diagnosed relatively recently [1,15,74,75]. The recovery scenarios plotted in Figs. 3–9 depend upon hormone sensitivities, fasting periods and rates being able to return to healthy values on recovery diets. In the model, the rate of lipid oxidation, the rate of lipolysis, the length of the fasting state, and leptin and insulin sensitivities are dependent on carbohydrate intake. All are assumed to decrease with increasing excess carbohydrate intake. In the original model, VLDL-TG clearance was also assumed to decrease with excess carbohydrate consumption. This assumption yielded higher

VLDL-TG at higher fat masses than seen in the DiRECT trial so was not implemented in the simulations shown in this study.

### 6.2. Comparison with published results

The model may be validated by comparison with type 2 diabetes remission trials and weight loss trials (short-term and long-term) and short-term weight gain or overfeeding trials. Comparisons for long-term weight gain simulations and data are limited to observations. Setting up a long-term weight gain experiment likely to result in ill-health would be unethical. The goal is to be able to predict time courses to health and disease, by using extremely detailed quantitative information, gathered over a variety of timescales, from many different experiments.

#### 6.2.1. Comparison with type 2 diabetes remission trials

The simulations presented correspond to an initially healthy individual, at the MCMF steady state, with a lean body mass of 60 kg, gaining weight on the HCMHF diet for six years, reaching a fat mass $F = 43.7$ kg, corresponding to a mass of 103.7 kg and a BMI of 36, assuming a height of 1.7 m. A change of diet, from the HCMHF diet to the LE diet (850 kcal/d) is predicted to result in rapid and concurrent decreases in HLipid and PLipid, with HLipid falling to the MCMF steady state healthy value in one to two weeks and PLipid falling to the MCMF steady state healthy value in six to nine weeks [15,16,73]. Remission from type 2 diabetes is predicted to be achieved in one week, due to the rapidly adjusting hepatic insulin sensitivity, consistent with experiment [7,15,16,73]. The redifferentiation of $\beta$-cells is predicted to take much longer, consistent with the results of a study into the return of $\beta$-cell function during the DiRECT trial [11]. In this study, it was found that a gradual increase in $\beta$-cell function, to a value similar to that shown by a non-diabetic control group, occurred over twelve months. In the simulations shown, $\beta$-cell function does not decrease to the point that improved hepatic insulin sensitivity cannot compensate, consistent with type 2 diabetes of shorter duration. Model predictions are consistent with observed rapid reductions in $G$, $I$ and triglycerides on very-low-calorie diets for overweight individuals with type 2 diabetes of shorter duration. Such investigations include the U.K. Counterpoint, Counterbalance and DiRECT trials [1,4,15,16,73], a Thai study [74] and a study done in Qatar (DIADEM-I) [75]. More detail is given below.

1. Weight loss: The Counterpoint study, reported in 2011 [15,73], had 11 obese subjects with type 2 diabetes, put on a 600 kcal/d type 2 diabetes remission diet. In one week, mean $G$ fell from 9.2 mmol/l (166 mg/dl, type 2 diabetes) to 5.9 mmol/l (106 mg/dl, remission), fasting plasma insulin halved, mean triglycerides fell from 2.4 mmol/l (212 mg/dl) to 1.2 mmol/l (106 mg/dl), HLipid fell by 30% (and by 70% in 4 weeks), and hepatic insulin sensitivity doubled. PLipid took 8 weeks to fall by 25%. Hence, remission may be achieved in one week. Model simulations are consistent with these observations.
2. Weight loss: During the Counterbalance study, 30 people with a type 2 diabetes duration between six months and 23 years followed a very low calorie diet (VLCD) for 8 weeks. All oral agents or insulin treatments were stopped at baseline. In the Counterbalance study (total energy intake 624–700 kcal/d), on average 15 kg was lost in 8 weeks. The (black) low energy simulations in Figs. 3–9 (total energy intake 850 kcal/d, modelling the DiRECT trial), predict a weight loss of 14 kg in 9 weeks, which is consistent with the experimental results.
   The reported results that show, after 8 weeks on the Counterbalance VLCD, for responders, mean triglycerides fell from 1.97 mmol/l (175 mg/dl) to 1.25 mmol/l (110 mg/dl), hepatic insulin sensitivity more than doubled, median basal HGP reduced by 8%, mean fasting serum insulin more than halved, mean $G$ fell from 8.9 mmol/l (160 mg/dl, type 2 diabetes) to 6.2 mmol/l (111 mg/dl, remission), HLipid fell to about 15% of baseline value, and both hepatic VLDL-TG production and PLipid also fell. Fig. 1 A in the Counterbalance report [4] shows a rapid increase in $G$, over one week, following an increase in dietary energy. Model simulations are consistent with these results.
   The rapid decrease in HLipid to healthy values in a few days/weeks, for the overweight on a VLDC, is also reported elsewhere, by the same authors [16,73].
   Responders on the Counterbalance diet reached a fat mass of 30.1% (of total body mass) after 8 weeks on the VLCD, and mostly maintained this weight, hepatic insulin sensitivity and remission for 6 months. Model simulations correspond to a person with lean body mass of 60 kg, and, after reducing from $F = 43$ to $F = 25$ on the black LE energy trajectory, that is reaching a fat mass of 29.4%, are predicted be able to maintain remission unless a HC weight-maintaining diet is chosen. Again, simulations are consistent with observation.
3. Weight loss: The DiRECT study, reported in 2018–2019, which followed the initial small Counterpoint and Counterbalance studies, was based on a slightly higher 850 kcal/d low energy diet, and is the basis for the simulations shown. The DiRECT data is reported at 12 mo and 24 mo [1,2]. The simulations shown (refer to the black low energy diet trajectory) are consistent with Counterpoint, Counterbalance and DiRECT trends, rapid lowering of $G$, $I$, HLipid, PLipid and slower lowering of $F$. They are consistent with the conclusion reached, that on average, subjects needed to lose approximately 15 kg fat mass to maintain remission. Note that the DiRECT study did not continue the diet for 12 mo, only for 3–5 mo, followed by stepped changes, reintroducing food, whilst trying to avoid weight gain.
   The model predictions are consistent with published results [2] concerning the variability and durability of remission success. See Section 5.6. Simulations predict that a fat mass loss of approximately 15 kg for individuals typical of those on the DiRECT trial would be associated with borderline success in achieving and maintaining remission from overweight type 2 diabetes, in the long term. The model predicts rapid remission on the initial short-term unsustainable low-energy remission trajectory.
4. Weight gain: The DiRECT trial [1,2], includes a baseline data summary relating to a population in the U.K. characterised by the diagnosis of type 2 diabetes in the previous six years. Baseline biomarker values $G$ (from $HbA_{1c}$), $F$ (from BMI), VLDL-TG (from triacylglycerol/triglycerol), and $I$, for the starting point for the remission simulations (in black) could have been inferred from the data summary. However, the preliminary red trajectory (follow the red HCMHF trajectory for six years) was included to demonstrate that the long-term weight gain predictions of the model, from health to disease, compare very favourably with the DiRECT trial baseline data for those who have had type 2 diabetes diagnosed in the previous six years, on a diet of excess energy. See Tables 4 and 5 in the report of the DiRECT trial clinical and metabolic features [2]. For example, by modelling a diet with excess CHO and excess lipid (the HCMHF diet) for six years, from the MCMF healthy state, one obtains a point in phase space with $G = 164$ mg/dl, $I = 0.5$ ng/ml, $F = 43.7$ kg, VLDL-TG = 203 mg TG/dl, and high hepatic and pancreatic lipids, consistent with observation. This is the point marked with a black pentagram on the red HCMFH trajectory. Of course, the biomarker time courses of the DiRECT trial participants prior to the trial are unknown, but there is nothing inconsistent in the modelling from health to disease and the available data. By using the model predictions, one also obtains a complete starting point for the (black) low energy (LE) trajectory, with eleven components.

#### 6.2.2. Further model comparison and validation

A previous version of the model was developed to compare LCHF and HCLF diets with respect to weight loss for the overweight with type 2 diabetes [8].

1. Weight loss over a few weeks: Model simulations [8, §5.2] matched the data from the trial by Hall et al. [82], over 4 weeks The model takes into account that rates of lipolysis, lipid oxidation, hormone sensitivities take time to adjust after a change of diet [12]. For example, on changing to a very low carbohydrate (LC) diet, ketosis may take days to weeks to stabilise [83–85]. The model simulations agreed with the experimental evidence, that fat mass loss on the LC diet over a few weeks was no faster than that experienced on the baseline high carbohydrate (HC) diet. However, fat mass loss is predicted to be faster over six months, on a LCHF diet compared to a HCLF diet, as summarised below.
   When changing from a LCHF or ketogenic diet to a HCLF diet, lipid oxidation rates will initially be high while TGin will be low. This change is likely to favour short-term fat mass loss, unlike the change from a HCLF diet to a LCHF or ketogenic diet (when at first lipid oxidation rates will initially be low while TGin will be high). Hence extrapolating fat mass losses from short-term fat mass loss trials lasting only a few days to a few weeks to longer time frames may not be appropriate, given that when changing from a HCLF diet to a LCHF or ketogenic diet or vice versa, initially, the LCHF approach is predicted to be relatively slow and the HCLF diet is predicted to be relatively fast [8, §5.2.2].
2. Weight loss over six months to two years: The robust weight loss trend predicted by the model (and reported earlier [8]) is the higher speed with which the LCHF trajectory approaches steady state. After six months, the LCHF diet is predicted to result in a lower fat mass, showing double the fat mass loss than the HCLF diet. After 1–2 years, this difference closes, the HCLF diet catching up. These predictions are in agreement with the observations made by the authors of meta-analyses of randomised controlled trials comparing LC and LF diets [86,87] and with observations [88–90].
3. VLDL-TG is a fast variable, changing rapidly in response to changes in CHOin, over days to weeks, see [26,91].
4. Hepatic steatosis (defined as at least 5% of organ mass as lipid) corresponds to HLipid at least 2.4 g/dl. The starting point for the (black) low energy trajectory has HLipid approximately equal to 3.2 g/dl, about double the healthy value at the MCMF steady state (1.5 g/dl). This is consistent with the evidence in [9,16,73].
5. Bariatric surgery for the obese or overweight (which results in calorie restriction) also initiates a loss of HLipid and PLipid as well as remission from type 2 diabetes. In one experiment, lipid content was measured at baseline and after 6 mo [81]. On average, about 75% of HLipid was lost and slightly over half of the PLipid. Bariatric surgery shows remission from type 2 diabetes in one week [6,15,76]. Model predictions (low energy diet trends) are consistent with these measurements.
6. Over five days of overfeeding CHO, it was recorded that HGP rose rapidly [12], in a dose-dependent way. Hence, the rapid rise in $G$ (due to elevated HGP) on the HCMHF diet is consistent with experiment.

### 6.3. Comparison with published hypotheses

#### 6.3.1. The twin cycle hypothesis

The model was formulated with the twin cycle hypothesis [16] in mind in which it is assumed that PLipid increases after HLipid has reached saturation on diets of excess energy. Interestingly, the simpler assumptions in the model are sufficient to obtain results in excellent agreement with observation. In the model, HLipid and PLipid increase and decrease concurrently on weight gain and weight loss diets, respectively. The effects of the gains or losses in these lipids occur on different timescales. Hepatic insulin sensitivity decreases rapidly (and hence hepatic glucose production increases rapidly) with increasing hepatic lipid (in as little as a few days to a few weeks) and vice versa. The elevated HGP corresponding to six years on the HCMHF weight gain trajectory is predicted to return to the MCMF steady state level after one week on the LE diet. The effect of changing pancreatic lipid levels on beta-cell differentiation is seen much later, after months to years. See Figs. 3–10.

#### 6.3.2. Calorie restriction, not weight loss, initiates remission from overweight type 2 diabetes

Model predictions are consistent with the observation that remission from type 2 diabetes occurs much faster than a loss of fat mass [6,15,16]. Given the timing, a loss of fat mass is not thought to be the cause of remission from overweight type 2 diabetes. Instead, modelling predicts that calorie restriction, such as the change to a weight loss diet or bariatric surgery, initiates both the remission and the associated weight loss. This change causes both $G$ and $F$ to fall, on different timescales, consistent with the many positive associations between weight loss and remission from overweight type 2 diabetes reported in the literature [5,10]. Weight loss is observed to follow rapid remission from type 2 diabetes after calorie restriction, both in dietary clinical trials [6,15,16] and after bariatric surgery [6,92,93]. Hence, the notion that weight loss initiates remission from type 2 diabetes is not supported.

#### 6.3.3. Personal fat thresholds

The concept of a personal fat threshold (PFT), below which remission would likely be maintained, is useful when advising patients [94] but needs to be treated with caution. The model predicts that a PFT depends on the lipid to carbohydrate content of the proposed final diet. The use of a personal energy consumption threshold has the same pitfalls. When choosing a final diet, the lipid to carbohydrate ratio needs to be considered as well as energy content. It was assumed that protein content is fixed and moderate in all diets except for the LE diet. The model predicts variation in remission success at a fixed fat mass loss due to variation in baseline characteristics and choice of diet; and also variation in remission success at a fixed target fat mass due to choice of diet. Predictions in remission success are consistent with observation [1].

### 6.4. Predicting the potential success of a diet

Assuming reasonable $\beta$-cell function, after few weeks on a recovery diet, fasting plasma glucose, plasma lipid and hormone levels reflect the steady state of the new diet. The current fat mass may not reflect the new steady state, since fast variables approach steady state months or years ahead of slower ones. Hence, after few weeks on a recovery diet, fasting plasma glucose, plasma lipid and hormone levels may be used to gauge the potential success of the new diet. The current fat mass may be a very poor indicator of the potential success of a diet. Even if $\beta$-cell function has declined on a trajectory to overweight type 2 diabetes, a subsequent rapid loss of hepatic lipid is predicted to result in rapidly increasing hepatic insulin sensitivity and rapidly decreasing hepatic glucose production, which in turn results in much improved (lower) fasting plasma glucose, lipid and hormone levels over a short period of time.

### 6.5. Why do so many patients relapse?

Is it reasonable to assume that, since fasting plasma levels of glucose, insulin and VLDL-TG are healthy, and have been healthy and stable for a few weeks or months on a new diet, that the current fat mass is also healthy? Modelling predicts the answer is no, that one big mistake is to assume that because $G$, $I$ and VLDL-TG are currently

healthy and have been healthy for some time (weeks or months or longer) that the current fat mass $F$ should be the final goal. Maintaining the current fat mass could result in exchanging a remission trajectory to health for a relapse trajectory to overweight type 2 diabetes. For example, given a moderate-energy diet, the model predicts that one should stay on the diet. If fat mass is far above the steady state value, it should gradually decline. Straying to higher energy consumption, especially to higher carbohydrate consumption, is risky.

The model predicts that leaving a low-energy diet on a diet of excess energy with a low ratio of lipid to carbohydrate is more likely to lead to relapse than an isocaloric diet with a high ratio of lipid to carbohydrate.

Advice that works for one person may not work for another, for example, the advice to lose 15 kg or to aim for a target fat mass. Success is predicted to depend on baseline characteristics and the carbohydrate and lipid content of the final diet, assuming fixed and moderate protein content.

### 6.6. Fast-slow analysis

Glucose, insulin and lipid dynamics involve processes happening on multiple timescales. A full model would include the daily fed state glucose and insulin fluctuations (on a very fast timescale of minutes to hours). These fluctuations have been omitted to provide the current long-term model, based on fasting values. The current long-term model shows three different timescales. For example, biomarker $G$ is fast (changing rapidly over days to weeks), $F$ is slow (changing over weeks to months), and $\beta$ is very slow. The situation is complicated by the fact that $G$ has a very slow component (due to changes in $\beta$-cell mass), as well as a fast component (due to changes in hepatic lipid and consequent changes in hepatic insulin sensitivity). Equations are written in terms of $F/F_0$. One could further non-dimensionalise the model and do a fast-slow-very slow analysis. However, the current long-term model does not show oscillations and so the analysis and trajectories as plotted provide a useful picture of the long-term dynamics. It is hoped that the graphs might be of interest to clinicians and that the fact that standard units for biomarkers have been used may be of benefit.

The current model could be extended to take account of the daily fed state fluctuations. However, the equations would become more complicated, since although CHO input and output would still be assumed to cancel over one day (see Section 3.4), the daily fed state fluctuations would now be of interest and could no longer be omitted. Hence, the fasting long-term model, as presented, could be viewed as a submodel of a model with four timescales (very fast, daily fed fluctuation over minutes and hours, not included in the current model), fast (changes in glucose over days to weeks as shown), slow (changes in fat mass over weeks to months as shown) and very slow (changes in differentiated $\beta$-cell mass as shown).

### 6.7. Sensitivity to dietary carbohydrate

A comparison of the trajectories for the isocaloric LCHF, MCMF and HCLF diets allows the reader to gauge the sensitivity of the simulations to the assumption that altering the CHO content of the diet has an effect on the fasting/fed hours, insulin and leptin sensitivities and rates of lipid oxidation and lipolysis. With reference to the MCMF diet, the LCHF diet corresponds to an increase in fasting hours and increases in insulin and leptin sensitivities and rates of lipid oxidation and lipolysis. The HCLF diet corresponds to the opposite scenario. The main effect is the faster speed at which the LCHF diet approaches steady state, compared to the HCLF diet, the MCMF diet being intermediate in speed. This effect is seen over weeks to months. These predictions are in agreement with the observations made by the authors of meta-analyses of randomised controlled trials comparing LC and LF diets [86,87] and with observations in [88–90].

The original model formulation [8] focussed on comparing these diets and reporting evidence for the assumptions made concerning CHO intake. Steady state values for diets of moderate energies do not differ substantially, see Fig. 9, and it was observed that differences in fat mass at steady state would probably be judged not statistically significant, if found experimentally (based on the literature, differences of only a few kilograms) [8, §5.2.1].

A comparison of the remission/relapse trajectories at a fixed (higher) fat mass also provides a sensitivity analysis to the effects of dietary CHO. For example, for $F \approx 20$ kg, a multiple of the LCHF diet is predicted to provide better glycaemic control, than a multiple of the HCLF diet. As $F$ is fixed at higher values, model predictions become more sensitive to the assumption that altering the CHO content of the diet has an effect on the fasting/fed hours, insulin and leptin sensitivities and rates of lipid oxidation and lipolysis. Trajectories were not plotted for fixed $F > 25$ kg in Fig. 5, for multiples of the HCLF diet, since the amount of CHO in the diet would mean extrapolating from the data in [12]. These diets are out of range of the model. Simulations at these higher fat masses, not shown, for multiples of the HCLF diet, suggest that the effect of dietary CHO on the fasting/fed hours, insulin and leptin sensitivities and rates of lipid oxidation and lipolysis, does not grow so fast, or at all, at higher multiples. Such a conjecture needs further investigation.

### 6.8. Limitations

This study does not apply to those individuals whose hormone sensitivities, fasting periods and rates of lipid oxidation and lipolysis do not return to healthy values on recovery diets. It does not take into account differences in lipid metabolism and storage due to differences in sex hormone profiles. It does not take into account that a small proportion of the population, possibly 10%, have parameters which are independent, or less dependent, on carbohydrate intake than assumed in this study [12]. It does not distinguish between different types of carbohydrate and lipid. The model may be adjusted to take account of all these factors, but this has not been done for this study.

In addition, this study assumes the parameter $F_0$, a lipolysis fat threshold, is fixed. This value represents a healthy fat mass in the context of the model. Replacing this fixed value with a range of healthy values enables the modelling of an increase in adiposity in the absence of type 2 diabetes on diets of excess energy and hence allows the modelling of the metabolically healthy but obese (MHO) phenotype. This is future work.

## 7. Conclusions

This article addresses the durability of remission from overweight type 2 diabetes from a modelling perspective: given certain weight loss advice, is remission predicted, and if so, how durable is it predicted to be? If subsequent relapse is predicted, how could it be prevented or minimised? It is a study in fast and slow variables.

The modelling predicts that a fat mass loss of approximately 15 kg for individuals typical of those on the DiRECT trial would be associated with borderline success in achieving and maintaining remission from overweight type 2 diabetes, in the long term. The model predicts rapid remission on the initial short-term unsustainable low-energy remission trajectory. Long-term success depends on the final sustainable diet chosen. If lipid is consumed in preference to carbohydrate, then durable remission is predicted at higher fat masses.

The modelling does not support the notion that fat mass loss itself generates the remission. Instead, the modelling predicts that fat mass loss and remission from type 2 diabetes are positively associated as they are both consequences of a change in diet and/or exercise plan. Assuming constant exercising habits and rates (lipolysis, lipid oxidation) and hormone sensitivities (insulin and leptin) that adjust with carbohydrate intake, a change to a diet lower in energy and no higher in carbohydrate content causes fat mass loss and a lowering of fasting plasma glucose, insulin and VLDL-TG levels. Fat mass loss

happens slowly. The lowering of fasting plasma glucose, insulin and VLDL-TG levels has a rapid component (linked to a fast reduction in hepatic lipid) and, in the case that $\beta$-cell function is recovering, a very slow component (linked to a fast reduction in pancreatic lipid which takes longer to have an effect). The cause of remission or relapse is the change in diet. This view of cause and effect, and an appreciation of slow and fast variables, helps to frame advice.

Modelling predicts that the fast biomarkers $G$, $I$ and VLDL-TG are good indicators of the potential success of the diet, with the caveat that a low-energy (and hence unsustainable) diet should only be followed until fat mass is healthy, no longer. The model predicts that a low-energy diet steady state fat mass could be very low. In this study, it is assumed that one would change from a low-energy diet to a moderate-energy diet before fat mass falls below healthy values. The potential success of the chosen diet can be judged a few weeks after starting by measuring $G$, $I$ and VLDL-TG. If the values are healthy, then the patient may assume that the diet is a reasonable long-term choice, with respect to lipid and carbohydrate content, unless it is a low-energy diet.

For overweight individuals with type 2 diabetes, the predicted and observed rapid lowering of $G$, $I$ and VLDL-TG after a change to a diet of moderate or low energy is excellent news. These healthy outcomes are both predicted and observed to precede a loss of fat mass. Such knowledge may encourage adherence to a new diet.

The timing assumptions in the model are simpler than those in the twin cycle hypothesis. In the model, the liver and pancreas fill rapidly and concurrently with lipid on a diet of excess energy. Similarly, these organs show lipid loss rapidly and concurrently with calorie restriction. The effects of the changes in lipid in these organs occur on different timescales. Hepatic insulin sensitivity decreases rapidly, and hence hepatic glucose production increases rapidly, with increasing hepatic lipid (over days to weeks) and vice versa. The effect of changing pancreatic lipid on beta-cell differentiation is seen much later. The two effects correspond to the fast and very slow components of fasting plasma glucose and insulin concentrations.

Simulations enable the classification of three different kinds of advice for overweight patients with type 2 diabetes seeking remission.

1. The risky option: follow a low-energy diet, then maintain fat mass once fasting plasma glucose, insulin and VLDL-TG levels have been stable and healthy for a few weeks. Relapse is predicted to follow short-term remission if the chosen fat mass is too high. The fat mass threshold depends on the lipid to carbohydrate ratio of the diet, assuming fixed and moderate protein content.
2. The fastest option: follow a low-energy diet for a few weeks, then change to a diet of moderate energy. Durable remission is predicted in one week in the scenarios investigated.
3. The simplest option: follow a diet of moderate energy. Durable remission is predicted in one to four weeks in the scenarios investigated, depending on the carbohydrate content of the final diet.

The relapse diets investigated in this study are weight-maintaining. However, relapse diets are not necessarily weight-maintaining. The steady state value of $G$ for the final diet determines the final outcome, remission or relapse. The model predicts that advice should be given in terms of parameters (diets), not variables. Given a diet, the steady state determines the long-term outcome. Hepatic lipids, pancreatic lipids, skeletal muscle lipids and plasma concentrations of glucose, insulin, leptin, glucagon, VLDL-TG and NEFA are predicted to adjust quickly to a new diet, in a few weeks. Fat mass is predicted to follow in time, over weeks, months and years. The differentiated $\beta$-cell mass is even slower to adjust to near steady state. The variables $G$ and $I$ have both a fast component and a very slow component, corresponding to fast changes in hepatic lipid and hepatic insulin sensitivity and to very slow changes in the mass of differentiated $\beta$-cells, respectively. Modelling suggests that one should choose the diet wisely, not the target fat mass, and be patient. A moderate energy diet is predicted to result in remission and is the simplest recovery option investigated.

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## CRediT authorship contribution statement

**Catherine Z.W. Hassell Sweatman:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Conceptualization.

## Declaration of competing interest

None.

## Data availability

Data used is available to the public in the references cited. Code will be made available on request.

## Appendix A. Insulin and leptin sensitivities

Insulin and leptin sensitivities are modelled dependent on both variables and parameters. The latter take account of diet. Other factors such as exercise and gut microbes may have an effect but are beyond the scope of this version of the model [95]. Exercise habits are assumed to be moderate and constant. The causes of loss of insulin sensitivity (resistance) have been investigated and debated for decades.

1. The cause may be chronic postprandial hyperinsulinemia on a HC diet [96], too much lipid in various organs, high levels of leptin in adipocytes, genetic, or a combination thereof. Elevated HGP occurs after only 5 days on a HC diet, a form of hepatic insulin resistance [13].
2. Low carbohydrate diets provide superior glycaemic control (increased insulin sensitivity) than high carbohydrate diets [97].
3. It was reported that severely obese patients with a high prevalence of diabetes or the metabolic syndrome lost more weight during six months on a carbohydrate-restricted diet than on a calorie and fat restricted diet, with a relative improvement in insulin sensitivity and triglyceride levels, even after adjustments for weight loss [98].
4. A diet that partially replaces carbohydrate with unsaturated fat may improve insulin sensitivity in a population at risk for cardiovascular disease [99]. This study was a randomised, controlled, three-period, crossover feeding study (the Omni Heart trial).
5. Meta-regression analyses show that $HbA_{1c}$, fasting glucose and triglycerides improved with lower carbohydrate content diets in patients with type 2 diabetes [100]. This demonstrates that hepatic insulin sensitivity improves (increases) on lower carbohydrate diets, since the higher hepatic insulin sensitivity lowers HGP [15]. Also, hepatic lipids decrease on lower carbohydrate content diets, resulting in lower fasting triglycerides.
6. In a small group of obese patients with type 2 diabetes, a low-carbohydrate diet followed for two weeks resulted in spontaneous reduction in energy intake to a level appropriate to their height; weight loss that was completely accounted for by reduced caloric intake; much improved 24-hour blood glucose profiles, insulin sensitivity, and $HbA_{1c}$; and decreased plasma triglyceride and cholesterol levels. The long-term effects of this diet, however, remain uncertain [37]. In practice, the LC diet

was achieved by reducing the carbohydrate content of the baseline usual diet, from 300 g/d to 20 g/d, fat and protein (although unrestricted) changed little. Insulin sensitivity improved by 75% in two weeks.

7. It is assumed that ectopic lipid accumulation in skeletal muscle, the liver and the pancreas impairs insulin sensitivity in these tissues [51,101].

In order to model the dependence on variables, for example peripheral insulin sensitivity decreasing with increasing ectopic muscle lipid, a function $f : [0,\infty) \to [0,\infty)$ is required such that $f(1) = 1$, $f$ is near to its maximum near $x = 1$ and $f$ decreases asymptotically to some smaller positive value, for example to 0.5, as $x \to \infty$. The following function was chosen, although others were investigated. The model behaviour was not found to depend on the exact function chosen. Let

$$f(x) = 0.5\left(\frac{n+1}{n+x^2}\right) + 0.5. \tag{A.1}$$

Then $f(0) = (\frac{0.5}{n}) + 1.0$, $f(1) = 1$ and $\lim_{x\to\infty} f(x) = 0.5$. The value $n = 3.24$ was chosen, giving $f(0) = 1.1543$.

Let $F_0$, $L_0$, $\text{NEFA}_0$, $\text{MLipid}_0$, $\text{HLipid}_0$, $\text{PLipid}_0$ and $\text{VLDL-TG}_0$ be typical healthy values for fat mass and fasting plasma leptin, NEFA, MLipid, HLipid, PLipid and VLDL-TG concentrations, roughly corresponding to the MCMF steady state variable values. Let $AS_I$, $PS_I$, $HS_I$ and $ACS_I$ be the reference insulin sensitivities for adipose tissue, peripheral (skeletal muscle) tissue, hepatic tissue and $\alpha$-cells (pancreatic cells which secrete glucagon), respectively. Then, for example, adipose tissue insulin sensitivity is modelled by $AS_I f_{AS_I} g_{AS_I}$ where the effect of variables is modelled by

$$f_{AS_I} = a_A(f(L/L_0))^{p_1} + (1 - a_A), \tag{A.2}$$

and $a_A \in [0,1]$. Setting $a_A = 0$ models no effect and setting $a_A = 1$ models the maximum effect considered here. Leptin is thought to be an insulin-sensitiser in leptin sensitive (usually non-obese) subjects [102] although prolonged exposure to higher levels of leptin is thought to lead to insulin insensitivity in adipocytes [103]. The insulin-sensitising effect of leptin may be partly due to leptin-induced increased oxidation of lipids.

The parameter dependence is modelled by the function $g$, which is defined in terms of CHO intake and which has a reference value equal to one. Let

$$y_{\text{CHO}} = \frac{\text{CHOin}}{\text{CHOin}_0} \tag{A.3}$$

denote a carbohydrate ratio. This yields a measure of carbohydrate intake, relative to a moderate reference quantity, $\text{CHOin}_0$. The latter would be expected to change with exercise habits. Let

$$g(x) = \frac{7/3}{7/3 + x^2} + 0.3 \tag{A.4}$$

so $g(0) = 1.3$, $g(1) = 1.0$ and $\lim_{x\to\infty} g(x) = 0.3$. The parameter dependence of the insulin and leptin sensitivities is modelled by $g(y_{\text{CHO}})$. Then adipose insulin sensitivity is modelled by $AS_I f_{AS_I} g$, peripheral insulin sensitivity is modelled by $PS_I f_{PS_I} g$ where

$$f_{PS_I} = a_P(f(\text{MLipid}/\text{MLipid}_0))^{p_2} + (1 - a_P), \tag{A.5}$$

hepatic insulin sensitivity is modelled by $HS_I f_{HS_I} g$ where

$$f_{HS_I} = a_H(f(\text{HLipid}/\text{HLipid}_0))^{p_3} + (1 - a_H) \tag{A.6}$$

and $\alpha$-cell insulin sensitivity is modelled by $ACS_I f_{ACS_I} g$ where

$$f_{ACS_I} = a_{AC}(f(\text{PLipid}/\text{PLipid}_0))^{p_4} + (1 - a_{AC}). \tag{A.7}$$

It is assumed that ectopic lipid accumulation in skeletal muscle, the liver and the pancreas impairs insulin sensitivity in these tissues [51, 101].

Leptin sensitivity is modelled by $S_L f_{S_L} g$, where

$$f_{S_L} = a_L(f(\text{VLDL-TG}/\text{VLDL-TG}_0))^{p_5}(f(F/F_0))^{p_6} + (1 - a_L) \tag{A.8}$$

represents a scaling of leptin sensitivity with VLDL-TG and $F$, since it has been reported that triglycerides induce leptin resistance at the blood–brain barrier [104] and observed that obese individuals appear to be leptin resistant [105]. Here $a_L \in [0,1]$. The independent scaling factor $S_L = 1$ in the reference scenario. The power of $f$ used determines the minimum value for the scaling term, for example, if $a_P = 1$, then $f_{PS_I}$ has a minimum of $0.5^{p_2}$. These powers may be altered to adjust the scale of the modulation. The values $p_1 = p_2 = p_3 = p_4 = 2$ and $p_5 = p_6 = 1$ and $a_A = a_P = a_H = a_{AC} = a_L = 1$ were used in this study.

Leptin sensitivity is difficult to measure, There is, as yet, no standard way to do this [106,107]. The very high values of leptin levels seen in obese people are considered to be a sign of loss of sensitivity (resistance) [103]. Factors considered to affect leptin sensitivity:

1. Hyperleptinemia is thought to cause leptin resistance [95]. Hence it could be conjectured that a HC diet, especially a high glycaemic index diet, could cause leptin resistance, given that high daily insulin concentrations stimulate high leptin secretion.
2. Overfeeding CHO in healthy women caused leptin levels to rise, but overfeeding of fat did not [107].
3. The removal of fructose from high fat diets can reverse leptin resistance and hyperleptinemia [107].
4. Evidence has shown that diet components are linked to the impairment of the leptin system. Diets high in fat, carbohydrates, and specific sugars, such as fructose and sucrose, as well as low in protein are associated with markers of leptin resistance [107].
5. LC diets are associated with lower insulin and leptin levels, and are thought to increase leptin sensitivity, assuming lipid intake is not excessive [36,37].
6. Physical exercise is thought to relieve endoplasmic reticulum stress thereby increasing leptin sensitivity [95].
7. High levels of VLDL-TG are thought to block leptin at the blood–brain barrier hence decreasing leptin sensitivity [104].
8. Physical exercise is thought to increase VLDL-TG clearance rates [108–110], thereby raising leptin sensitivity.
9. A higher fat mass secretes more leptin [103] and hence may cause a loss of leptin sensitivity via hyperleptinemia [107].
10. Inflammation of the hypothalamus is associated with obesity and can cause leptin resistance [95].
11. Hypertrophic adipocytes secrete more leptin and the leptin to adiponectin ratio was found to be a potentially useful measure of insulin resistance. In summary, leptin and insulin resistance seem to occur together [39].

In the model, leptin sensitivity is assumed to change on the following timescales

1. fast, with CHOin, via $g(y_{\text{CHO}})$, since $y_{\text{CHO}}$ is assumed to adjust from one diet to another in a matter of a few weeks (see Appendix B)
2. fast, with VLDL-TG, via $(f(\text{VLDL-TG}/\text{VLDL-TG}_0))^{p_5}$
3. and slow, with $F$, via $(f(F/F_0))^{p_6}$.

## Appendix B. Modelling transient changes in parameters

Transient changes in parameters that may occur when changing from one diet to another should not be ignored in short-term modelling. For example, when changing from an old diet to a new diet, leptin sensitivity and adipocyte, peripheral, hepatic and $\alpha$-cell insulin sensitivities, the rate of lipid oxidation, the rate of lipolysis and VLDL-TG clearance rates may take some days or weeks to adjust, depending on the diets and the individual. To take account of short term transients caused by altering carbohydrate intake, sensitivities and rates were replaced by

time dependent versions, assuming settling times of 3–4 weeks. Phinney and co-workers have found that it takes at least one week and possibly more than six weeks (the duration of their trial) to adapt to ketosis, during which lipid oxidation and lipolysis rates change [83–85]. These transient changes are of no consequence when determining steady state variable values but do alter short-term time courses. More background may be found in the original model description [8]. In summary, $g(y_{\mathrm{CHO}})$ was replaced by a function $\tilde{g}(\mathrm{CHOin}_{\mathrm{previous}}, \mathrm{CHOin}_0, \mathrm{CHOin}, t)$, abbreviated to $\tilde{g}(t)$, where

$$\tilde{g}(t) = \frac{c}{1+e^{-kt}} + d \tag{B.1}$$

$c = 2(g(y_{\mathrm{CHO}}) - g(y_{\mathrm{CHO,previous}}))$, $d = 2g(y_{\mathrm{CHO,previous}}) - g(y_{\mathrm{CHO}})$, $k = 0.01$,

$$y_{\mathrm{CHO,previous}} = \frac{\mathrm{CHOin}_{\mathrm{previous}}}{\mathrm{CHOin}_0} \tag{B.2}$$

and $\mathrm{CHOin}_{\mathrm{previous}}$ is the carbohydrate intake for the previous diet. Then

$$\tilde{g}(0) = g(\frac{\mathrm{CHOin}_{\mathrm{previous}}}{\mathrm{CHOin}_0}) \quad \text{and} \lim_{t\to\infty} \tilde{g}(t) = c + d = g(\frac{\mathrm{CHOin}}{\mathrm{CHOin}_0}).$$

## Appendix C. Lipid oxidation and lipolysis rates

Lipid oxidation and lipolysis rates were estimated from published experimental data [12] by quadratic regression to obtain

$$r_{Lox}(x) = (5.291 \times 10^{-7}x^2 - 0.00242222x + 1.51926)/0.79$$

and

$$r_{Ll}(x) = (7.3796 \times 10^{-7}x^2 - 0.00213275x + 1.92354)(152.80)/1.31$$

where

$$x = \frac{342 \times \mathrm{CHOin}}{\mathrm{CHOin}_0}.$$

To take account of a change of diet, time dependent versions of $r_{Lox}$ and $r_{Ll}$ were used in the simulations, defined in a similarly way to $\tilde{g}(t)$. See Appendix B.

## Appendix D. Lipid housekeeping at reference parameters

The following assumptions were made [8]. Triglyceride intake into adipocytes is due to the arrival of dietary chylomicron triglyceride (CM-TG, fed) and VLDL-TG (fed and fasting). The daily rate of appearance of CM-TG is called TGin in the model. TGin is shared between tissues as detailed below. The reference daily dietary triglyceride intake $\mathrm{TGin}_0$ = 100 g [35]. This is partitioned, assuming a healthy reference state, as

1. 45 g to adipose tissue [35],
2. 23 g TG converted to NEFA spillover, since spillover fatty acids may constitute 40%–50% of the total plasma NEFA pool in the postprandial period [32,57]; delivering 5 g to liver, 16 g to muscle and 2 g to heart,
3. 25 g as CM-TG remnants (TG to liver on chylomicron remnants [35])
4. and 7 g CM-TG to skeletal muscle.

Skeletal muscle daily

1. receives $0.07 \times$ TGin (as CM-TG), 7 g (fed),
2. $(16/23) \times 0.23 \times$ TGin, spillover, 16 g (fed),
3. 29 g TG equivalent from NEFA, (fasting, Ref. [35] gives 20 g as an estimate)
4. and 10 g TG from VLDL (fed and fasted, see Section 3.11).
5. The sum of VLDL-TG and CM-TG is 17 g, [35] gives 10 g as an estimate.
6. Losses due to $\beta$-oxidation are assumed to be 62 g,
7. equating to 62 g TG in and out.

Pancreatic lipid balance is modelled on skeletal muscle lipid balance, with the addition of PDNL. The amounts are scaled by the ratio of organ masses, assuming skeletal muscle mass is half LBM.

Hepatic TG balance: The liver daily

1. receives $0.25 \times$ TGin (as CM-TG remnants), 25 g (fed) [35],
2. receives $0.22 \times 0.23 \times$ TGin, spillover, 5 g (fed),
3. and receives NEFA, assuming 10% recycled to adipose tissue, then 32% of the remainder is delivered to the liver, equivalent to 19 g TG (fasting) [35],
4. makes 1 g TG (HDNL) [12,35],
5. loses 20 g TG secreted on VLDL (total production of VLDL-TG in nondiabetics given as 250 mg per day per kg [59]), assuming 8 g fed and 12 g fasted [60],
6. and loses 30 g TG through $\beta$-oxidation (balances intake),
7. equating to 50 g TG in and out [61].

Adipose tissue daily

1. receives $0.45 \times$ TGin (as CM-TG, fed),
2. and 10 g TG from VLDL, fed and fasted, since approximately 50% of VLDL-TG is oxidised and 50% is stored [53],
3. makes 1 g ADNL [12,33], inhibited by leptin [103] and glucagon [111] and stimulated by insulin (fed) [32,112] and CHO consumption [12]
4. loses 66 g due to lipolysis [33], inhibited by insulin, this rises with excess fat mass (fasted)
5. recycles 10%, that is 6 g, of the lipolysed TG back to adipose TG [113]
6. the 60 g TG lipolysed and not recycled comprises 29 g to skeletal muscle, 19 g to liver [35] 12 g to heart [114]
7. and loses 4 g through $\beta$-oxidation, scaled by fat mass (balances intake)
8. equating to 62 g TG in and out.

Plasma VLDL-TG balance: The blood daily

1. receives 20 g from liver,
2. delivers 10 g to skeletal muscle, 10 g to adipose tissue, see Section 3.11,
3. equating to 20 g TG in and out.

Plasma NEFA balance: The blood daily

1. receives the equivalent of 60 g TG as NEFA from adipose tissue, delivering 29 g to skeletal muscle, 19 g to liver, 12 g to heart
2. receives the equivalent of 23 g TG as NEFA from spillover, delivering 5 g to liver, 16 g to muscle and 2 g to heart.
3. equating to 83 g TG in and out.

These estimated values would be expected to change with changes in diet and associated hormone concentrations and sensitivities.

## Appendix E. Model comparison

A 2008 study of the dynamics of human body weight change [115] describes a model of changes in energy in the body and models three biomarkers, namely fat, protein and glycogen. Protein and glycogen are combined into lean mass. The 2008 model is compared to the model described in this article, the 2023 model, with eleven biomarkers. In the 2008 model, glycogen stores are ignored in the long-term modelling (as in the 2023 model). The fast dynamics (daily fluctuations in the fed state) are averaged out, leaving the slower dynamics (as in the 2023 model). An assumption [115, equation 12] is made that means one cannot model fat mass increasing while lean mass is constant (undefined derivative). The 2023 model does allow for such a scenario, in fact it assumes such a scenario, although it could be generalised to include lean body mass changing in time. Two recent studies on the

durability of type 2 diabetes remission using a very low carbohydrate diet (VLCD) show changes in lean body mass are very small (of the order of 1 kg) while change in fat mass are significant (of the order of 10 kg) over a few weeks of a VLDC [74,75]. Hence the two models differ substantially.

The two models also take different approaches to simplifying the model equations. The 2008 model takes a moving average over days, while the 2023 model simply assumes all CHO consumed is oxidised, stored as glycogen or converted to lipid over one day.

The 2008 study describes two classes of model, the first class has one unique body composition and mass per diet and energy expenditure, at stable steady state. In the second class, per diet and energy expenditure, there is a continuous curve of fixed points, described as an invariant manifold, with an infinite number of possible body compositions and masses at steady state. In the 2023 model, a spectrum of fat mass at the same energy intake may be obtained, at steady state, by varying the CHO to lipid ratio (one parameter steady state continuation). Lean mass is assumed constant. Such a continuation curve (not shown) could be considered an invariant manifold with respect to energy consumption. For example, the steady states for the LCHF, MCMF and HCMF diets are points on such a continuation curve.

The authors of the 2008 model state that there does not seem to be evidence of multiple fixed (stable, physiological) points or invariant manifolds as described. Steady state behaviour can change when models are reduced to lower dimensions, using one variable as a proxy for another; or when increased to higher dimensions, no longer using one variable as a proxy for another. It is possible that, in reducing dimensions, the steady state behaviour in the 2008 model has changed. For example, in the Topp model [22], a limit point exists, at physiological values of biomarkers. However, this disappears when glucotoxity is no longer used as a proxy for lipotoxicity ($d\beta/dt$ is no longer a quadratic equation in $G$, instead it depends on both PLipid and $G$).

In summary, the two models show both differences and similarities as well as different approaches.

## References


[1] M.E.J. Lean, W.S. Leslie, A.C. Barnes, N. Brosnahan, G. Thom, L. McCombie, C. Peters, S. Zhyzhneuskaya, A. Al-Mrabeh, K.G. Hollingsworth, A.M. Rodrigues, L. Rehackova, A.J. Adamson, F.F. Sniehotta, J.C. Mathers, H.M. Ross, Y. McIlvenna, P. Welsh, S. Kean, I. Ford, A. McConnachie, C.M. Messow, N. Sattar, R. Taylor, Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial, Lancet Diabetes Endocrinol. 7 (5) (2019) 344–355, http://dx.doi.org/10.1016/S2213-8587(19)30068-3.

[2] M.E.J. Lean, W.S. Leslie, A.C. Barnes, N. Brosnahan, G. Thom, L. McCombie, C. Peters, S. Zhyzhneuskaya, A. Al-Mrabeh, K.G. Hollingsworth, A.M. Rodrigues, L. Rehackova, A.J. Adamson, F.F. Sniehotta, J.C. Mathers, H.M. Ross, Y. McIlvenna, R. Stefanetti, M. Trenell, P. Welsh, S. Kean, I. Ford, A. McConnachie, N. Sattar, R. Taylor, Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial, Lancet 391 (10120) (2018) 541–551, http://dx.doi.org/10.1016/S0140-6736(17)33102-1.

[3] J.L. Unick, et al., Effectiveness of lifestyle interventions for individuals with severe obesity and type 2 diabetes, Diabetes Care 34 (10) (2011) 2152–2157, http://dx.doi.org/10.2337/dc11-0874.

[4] S. Steven, K.G. Hollingsworth, A. Al-Mrabeh, L. Avery, B. Aribisala, M. Caslake, R. Taylor, Very low-calorie diet and 6 months of weight stability in type 2 diabetes: Pathophysiological changes in responders and nonresponders, Diabetes Care 39 (5) (2016) 808–815, http://dx.doi.org/10.2337/dc15-1942.

[5] J. Tay, N.D. Luscombe-Marsh, C.H. Thompson, M. Noakes, J.D. Buckley, G.A. Wittert, W.S. Yancy Jr., G.D. Brinkworth, Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial, Am. J. Clin. Nutr. 102 (4) (2015) 780–790, http://dx.doi.org/10.3945/ajcn.115.112581.

[6] S. Juray, K.V. Axen, S.E. Trasino, Remission of type 2 diabetes with very low-calorie diets — a narrative review, Nutrients 13 (6) (2021) 2086, http://dx.doi.org/10.3390/nu13062086.

[7] H. Yki-Järvinen, Type 2 diabetes: remission in just a week, Diabetologia 54 (2011) 2477–2479, http://dx.doi.org/10.1007/s00125-011-2266-6.

[8] C.Z.W. Hassell Sweatman, Mathematical model of diabetes and lipid metabolism linked to diet, leptin sensitivity, insulin sensitivity and VLDLTG clearance predicts paths to health and type II diabetes, J. Theoret. Biol. 486 (2020) 110037, http://dx.doi.org/10.1016/j.jtbi.2019.110037.

[9] R. Taylor, Type 2 diabetes remission: latest evidence for health care professionals, Pract. Diabetes 37 (5) (2020) 177–182, http://dx.doi.org/10.1002/pdi.2297.

[10] R. Taylor, A. Ramachandran, W.S. Yancy, N.G. Forouhi, Nutritional basis of type 2 diabetes remission, BMJ 374 (2021) http://dx.doi.org/10.1136/bmj.n1449, n:1449.

[11] S.V. Zhyzhneuskaya, A. Al-Mrabeh, C. Peters, A. Barnes, B. Aribisala, K.G. Hollingsworth, A. McConnachie, N. Sattar, M.E.J. Lean, R. Taylor, Time course of normalization of functional $\beta$-cell capacity in the diabetes remission clinical trial after weight loss in type 2 diabetes, Diabetes Care 43 (2020) 813–820, http://dx.doi.org/10.2337/dc19-0371.

[12] J.M. Schwarz, R.A. Neese, S. Turner, D. Dare, M.K. Hellerstein, Short-term alterations in carbohydrate energy intake in humans. striking effects on hepatic glucose production, de novo lipogenesis, lipolysis, and whole-body fuel selection, J. Clin. Invest. 96 (6) (1995) 2735–2743, http://dx.doi.org/10.1172/JCI118342.

[13] M.K. Hellerstein, J.M. Schwarz, R.A. Neese, Regulation of hepatic de novo lipogenesis in humans, Annu. Rev. Nutr. 16 (1996) 523–557, http://dx.doi.org/10.1146/annurev.nu.16.070196.002515.

[14] R. Taylor, Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause, Diabetologia 51 (2008) 1781–1789, http://dx.doi.org/10.1007/s00125-008-1116-7.

[15] E.L. Lim, K.G. Hollingsworth, B. Aribisala, M.J. Chen, J.C. Mathers, R. Taylor, Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol, Diabetologia 54 (10) (2011) 2506–2514, http://dx.doi.org/10.1007/s00125-011-2204-7.

[16] R. Taylor, Calorie restriction and reversal of type 2 diabetes, Expert Rev. Endocrinol. Metab. 11 (6) (2016) 521–528, http://dx.doi.org/10.1080/17446651.2016.1239525.

[17] C. Talchai, S. Xuan, H.V. Lin, L. Sussel, D. Accili, Pancreatic $\beta$-cell dedifferentiation as a mechanism of diabetic beta cell failure, Cell 150 (6) (2012) 1223–1234, http://dx.doi.org/10.1016/j.cell.2012.07.029.

[18] S. Efrat, Beta-cell dedifferentiation in type 2 diabetes: Concise review, Stem Cells 37 (10) (2019) 1267–1272, http://dx.doi.org/10.1002/stem.3059.

[19] M. Diedisheim, et al., Modeling human pancreatic beta cell dedifferentiation, Mol. Metab. 10 (2018) 74–86, http://dx.doi.org/10.1016/j.molmet.2018.02.002.

[20] A.S. Jackson, I. Janssen, X. Sui, T.S. Church, S.N. Blair, Longitudinal changes in body composition associated with healthy ageing: men, aged 20–96 years, Br. J. Nutr. 107 (2012) 1085–1091, http://dx.doi.org/10.1017/S0007114511003886.

[21] R.A. DeFronzo, Pathogenesis of type 2 diabetes mellitus, Med. Clin. North Am. 88 (4) (2004) 787–835, http://dx.doi.org/10.1016/j.mcna.2004.04.0131.

[22] B. Topp, K. Promislow, G. deVries, R.M. Miura, A.T. Finegood, A model of $\beta$-cell mass, insulin and glucose kinetics: pathways to diabetes, J. Theoret. Biol. 206 (4) (2000) 605–619, http://dx.doi.org/10.1006/jtbi.2000.2150.

[23] S.E. Kahn, R.L. Prigeon, D.K. McCulloch, E.J. Boyko, R.N. Bergman, M.W. Schwartz, J.L. Neifing, W.K. Ward, J.C. Beard, J.P. Palmer, Quantification of the relationship between insulin sensitivity and $\beta$-cell function in human subjects: Evidence for a hyperbolic function, Diabetes 42 (11) (1993) 1663–1672, http://dx.doi.org/10.2337/diab.42.11.1663.

[24] A. Caumo, P. Vicini, C. Cobelli, Is the minimal model too minimal? Diabetologia 39 (8) (1996) 997–1000, http://dx.doi.org/10.1007/BF00403922.

[25] C.B. Newgard, et al., A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance, Cell Metab. 9 (4) (2009) 311–326, http://dx.doi.org/10.1016/j.cmet.2009.02.002.

[26] E.J. Parks, R.M. Krauss, M.P. Christiansen, R.A. Neese, M.K. Hellerstein, Effects of a low-fat, high-carbohydrate diet on VLDL-triglyceride assembly, production, and clearance, J. Clin. Invest. 104 (8) (1999) 1087–1096, http://dx.doi.org/10.1172/JCI6572.

[27] S. Klein, S.W. Coppack, V. Mohamed-Ali, M. Landt, Adipose tissue leptin production and plasma leptin kinetics in humans, Diabetes 45 (7) (1996) 984–987, http://dx.doi.org/10.2337/diab.45.7.9848.

[28] G.C. Weir, S. Bonner-Weir, Five stages of evolving $\beta$-cell dysfunction during progess to diabetes, Diabetes 53 (Suppl 3) (2004) S16–S21, http://dx.doi.org/10.2337/diabetes.53.suppl_3.S16.

[29] Eli Lilly and Company, Information for the physician: Glucagon for injection (rDNA origin), 2023, https://pi.lilly.com/ca/glucagon-ca-pmi.pdf, PA 2286 AMP, revised April 25 2020. (Last Accessed 8 August 2023).

[30] B.R. Barrows, E.J. Parks, Contributions of different fatty acid sources to very low-density lipoprotein-triacylglycerol in the fasted and fed states, J. Clin. Endocrinol. Metab. 91 (4) (2006) 1446–1452, http://dx.doi.org/10.1210/jc.2005-1709.

[31] A.C. Pratt, J.A.D. Wattis, A.M. Salter, Mathematical modelling of hepatic lipid metabolism, Math. Biosci. 262 (2015) 167–181, http://dx.doi.org/10.1016/j.mbs.2014.12.012.

[32] F. Karpe, J.R. Dickmann, K.N. Frayn, Fatty acids, obesity and insulin resistance: time for a reevaluation, Diabetes 60 (10) (2011) 2441–2450, http://dx.doi.org/10.2337/db11-0425.

[33] A. Strawford, F. Antelo, M. Christiansen, M.K. Hellerstein, Adipose tissue triglyceride turnover, de novo lipogenesis, and cell proliferation in humans measured with $2H_20$, Am. J. Physiol. Endocrinol. Metab. 286 (4) (2004) E577–E588, http://dx.doi.org/10.1152/ajpendo.00093.2003.

[34] L.A. Rowland, et al., De novo lipogenesis fuels adipocyte autophagosome and lysosome membrane dynamics, Nature Commun. 14 (2023) 1362, http://dx.doi.org/10.1038/s41467-023-37016-8.

[35] K.N. Frayn, P. Arner, H. Yki-Järvinen, Fatty acid metabolism in adipose tissue, muscle and liver in health and disease, Essays Biochem. 42 (2006) 89–103, http://dx.doi.org/10.1042/bse0420089.

[36] C. Zinn, J. McPhee, N. Harris, M. Williden, K. Prendergast, G. Schofield, A 12-week low carbohydrate high fat (LCHF) diet improves metabolic health outcomes over a control diet in a randomised controlled trial with overweight defence force personnel, Appl. Physiol. Nutr. Metab. 42 (11) (2017) 1158–1164, http://dx.doi.org/10.1139/apnm-2017-0260.

[37] G. G. Boden, C. Sargrad, M. Homko, K. Mozzoli, T.S. Stein, Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes, Ann. Intern. Med. 142 (6) (2005) 403–411, http://dx.doi.org/10.7326/0003-4819-142-6-200503150-00006.

[38] J.V. Silha, M. Krsek, J.V. Skrha, P. Sucharda, B.L.G. Nyomba, L.J. Murphy, Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance, Eur. J. Endocrinol. 149 (2003) 331–335, http://dx.doi.org/10.1530/eje.0.1490331.

[39] F.M. Finucane, Correlation of the leptin:adiponectin ratio with measures of insulin resistance in non-diabetic individuals, Diabetologia 52, http://dx.doi.org/10.1007/s00125-009-1508-3.

[40] S. Gill, S. Panda, A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits, Cell Metab. 22 (2015) 789–798, http://dx.doi.org/10.1016/j.cmet.2015.09.005.

[41] V.D. Longo, S. Panda, Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan, Cell Metab. 23 (2016) 1048–1059, http://dx.doi.org/10.1016/j.cmet.2016.06.001.

[42] H.C. Denroche, K.K. Huynh, T.J. Kieffer, The role of leptin in glucose homeostasis, J. Diabetes Investig. 3 (2) (2012) 115–129, http://dx.doi.org/10.1111/j.2040-1124.2012.00203.x.

[43] J.P. German, J.P. Thaler, B.E. Wisse, S. Oh-I, D.A. Sarruf, M.E. Matsen, J.D. Fischer, G.J. Taborsky, M.W. Schwartz, G.J Morton, Leptin activates a novel CNS mechanism for insulin-independent normalization of severe diabetic hyperglycemia, Endocrinology 152 (2) (2011) 394–404, http://dx.doi.org/10.1210/en.2010-0890.

[44] G.C. Weir, S. Bonner-Weir, Islet $\beta$-cell mass in diabetes and how it relates to function, birth and death, Ann. New York Acad. Sci. 1281 (1) (2013) 92–105, http://dx.doi.org/10.1111/nyas.12031.

[45] J. Retzlaff, W. Newlon Tauxe, J.M. Kiely, C.F. Stroebel, Erythrocyte volume, plasma volume, and lean body mass in adult men and women, Blood 33 (5) (1969) 649–667, http://dx.doi.org/10.1182/blood.V33.5.649.649.

[46] J.A. Cases, I. Gabriely, X.H. Ma, X.M. Yang, T. Michaeli, N. Fleischer, L. Rossetti, N. Barzilai, Physiological increase in plasma leptin markedly inhibits insulin secretion in vivo, Diabetes 50 (2) (2001) 348–352, http://dx.doi.org/10.2337/diabetes.50.2.348.

[47] R.N. Bergman, D.T. Finegood, S.E. Kahn, The evolution of $\beta$-cell dysfunction and insulin resistance in type 2 diabetes, Eur. J. Clin. Invest. 32 (2002) 35–45, http://dx.doi.org/10.1046/j.1365-2362.32.s3.5.x.

[48] S.M. Darby, M.L. Miller, R.O. Allen, M. LeBeau, A mass spectrometric method for quantitation of intact insulin in blood samples, J. Anal. Toxicol. 25 (1) (2001) 8–14, http://dx.doi.org/10.1093/jat/25.1.8.

[49] C.A. Burtis, E.R. Ashwood, D.E. Bruns, Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, fourth ed., Elsevier, 2006.

[50] R.H. Unger, A.D. Cherrington, Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover, J. Clin. Invest. 122 (2) (2012) 4–12, http://dx.doi.org/10.1172/JCI60016.

[51] R. Taylor, A. Barnes, Translating aetiological insight into sustainable management of type 2 diabetes, Diabetologia 61 (2) (2018) 273–283, http://dx.doi.org/10.1007/s00125-017-4504-z.

[52] T.J. Kieffer, J.H. Habener, The adipoinsular axis: effects of leptin on pancreatic $\beta$-cells, Am. J. Physiol. Endocrinol. Metab. 278 (1) (2000) E1–E14, http://dx.doi.org/10.1152/ajpendo.2000.278.1.E1.

[53] I.R. Andersen, E. Søndergaard, L.P. Sørensen, B. Nelleman, L.C. Gormsen, M.D. Jensen, S. Nielsen, Increased VLDL-TG fatty acid storage in skeletal muscle in men with type 2 diabetes, J. Clin. Endocrinol. Metab. 102 (3) (2017) 831–839, http://dx.doi.org/10.1210/jc.2016-2979.

[54] P. Chakrabarti, J.Y. Kim, M. Singh, Y.-K. Shin, J. Kim, J. Kumbrink, Y. Wu, M.-J. Lee, K.H. Kirsch, S.K. Fried, K.V. Kandror, Insulin inhibits lipolysis in adipocytes via the evolutionarily conserved mTORC1-Egr1-ATGL-mediated pathway, Mol. Cell. Biol. 33 (18) (2013) 3659–3666, http://dx.doi.org/10.1128/MCB.01584-12.

[55] W. Zeng, R.M. Pirzgalska, M.M.A. Pereira, G.G. Martins, J.M. Friedman, A.I. Domingos, Sympathetic neuro-adipose connections mediate leptin-driven lipolysis, Cell 163 (1) (2015) 84–94, http://dx.doi.org/10.1016/j.cell.2015.08.055.

[56] J.H. Stern, J.M. Rutkowski, P.E. Scherer, Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk, Cell Metab. 23 (5) (2016) 770–784, http://dx.doi.org/10.1016/j.cmet.2016.04.011.

[57] S.E. McQuaid, L. Hodson, M.J. Neville, A.L. Dennis, J. Cheeseman, S.M. Humphreys, T. Ruge, M. Gilbert, B.A. Fielding, K.N. Frayn, F. Karpe, Down-regulation of adipose tissue fatty acid trafficking in obesity a driver for ectopic fat deposition?, Diabetes 60 (1) (2011) 47–55, http://dx.doi.org/10.2337/db10-0867.

[58] M.G. Myers Jr., R.L. Leibel, M.W. Schwartz, Obesity and leptin resistance: distinguishing cause from effect, Trends Endocrinol. Metab. 21 (11) (2010) 643–651, http://dx.doi.org/10.1016/j.tem.2010.08.002.

[59] M. Adiels, M.-R. Taskinen, C. Packard, M.J. Caslake, A. Soro-Paavonen, J. Westerbacka, S. Vehkavaara, A. Häkkinen, S.-O. Olofsson, H. Yki-Järvinen, J. Borén, Overproduction of large VLDL particles is driven by increased liver fat content in man, Diabetologia 49 (4) (2006) 755–765, http://dx.doi.org/10.1007/s00125-005-0125-z.

[60] M.T. Timlin, E.J. Parks, Temporal pattern of de novo lipogenesis in the prandial state in healthy men, Am. J. Clin. Nutr. 81 (1) (2005) 35–42, http://dx.doi.org/10.1093/ajcn/81.1.35.

[61] J.C. Cohen, J.D. Horton, H.H. Hobbs, Human fatty liver disease: old questions and new insights, Science 332 (6037) (2005) 1519–1523, http://dx.doi.org/10.1126/science.1204265.

[62] V.T. Samuel, G.I. Shulman, The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux, J. Clin. Invest. 126 (1) (2016) 12–22, http://dx.doi.org/10.1172/JCI77812.

[63] S.B. Biddinger, et al., Hepatic insulin resistance is sufficient to produce dyslipidemia and susceptibility to atherosclerosis, Cell Metab. 7 (2) (2008) 125–134, http://dx.doi.org/10.1016/j.cmet.2007.11.013.

[64] M.S. Brown, J.L. Goldstein, Selective versus total insulin resistance: a pathogenic paradox, Cell Metab. 7 (2) (2008) 95–96, http://dx.doi.org/10.1016/j.cmet.2007.12.009.

[65] R.F. Johansen, E. Søndergaard, L.P. Sørensen, A.G. Jurik, J.S. Christiansen, S. Nielsen, Basal and insulin-regulated VLDL1 and VLDL2 kinetics in men with type 2 diabetes, Diabetologia 59 (4) (2016) 833–843, http://dx.doi.org/10.1007/s00125-015-3856-5.

[66] F. Diraison, P. Moulin, M. Beylot, Contribution of hepatic de novo lipogenesis and reesterification of plasma non esterified fatty acids to plasma triglyceride synthesis during non-alcoholic fatty liver disease, Diabetes Metab. 29 (5) (2003) 478–485, http://dx.doi.org/10.1016/s1262-3636(07)70061-7.

[67] F.K. Huynh, U.H. Neumann, Y. Wang, B. Rodrigues, T.J. Kieffer, S.D. Covey, A role for hepatic leptin signaling in lipid metabolism via altered very low density lipoprotein composition and liver lipase activity in mice, Hepatology 57 (2) (2013) 543–554, http://dx.doi.org/10.1002/hep.26043.

[68] W. Huang, N. Dedousis, A. Bandi, G.D. Lopaschuk, R.M. O'Doherty, Liver triglyceride secretion and lipid oxidative metabolism are rapidly altered by leptin in vivo, Endocrinology 147 (3) (2006) 1480–1487, http://dx.doi.org/10.1210/en.2005-0731.

[69] J.D. Browning, J.A. Baker J., J. Rogers, S. Davis, T. Satapati, S.C. Burgess, Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction, Am. J. Clin. Nutr. 95 (5) (2011) 1048–1052, http://dx.doi.org/10.3945/ajcn.110.007674.

[70] D.M. Muoio, G.L. Dohn, F.T. Fiedorek, E.B. Tapscott, R.A. Coleman, Leptin directly alters lipid partitioning in skeletal muscle, Diabetes 46 (8) (1997) 1360–1363, http://dx.doi.org/10.2337/diab.46.8.1360.

[71] M.J. Watt, A.J. Hoy, Lipid metabolism in skeletal muscle: generation of adaptive and maladaptive intracellular signals for cellular function, Am. J. Physiol. Endocrinol. Metab. 302 (11) (2012) E1315–E1328, http://dx.doi.org/10.1152/ajpendo.00561.2011.

[72] M.G. Sandberg, J. Fridriksson, L. Madsen, V. Rishi, C. Vinson, H. Holmsen, R.K. Berge, S. Mandrup, Glucose-induced lipogenesis in pancreatic $\beta$-cells is dependent on SREBP-1, Mol. Cell. Endocrinol. 240 (2005) 94–106, http://dx.doi.org/10.1016/j.mce.2005.05.005.

[73] R. Taylor, Reversing type 2 diabetes, Pract. Diabetes 28 (9) (2011) 377–378, http://dx.doi.org/10.1002/pdi.1639.

[74] M. Umphonsathien others, Immediate and long-term effects of a very-low-calorie diet on diabetes remission and glycemic control in obese Thai patients with type 2 diabetes mellitus, Food Sci. Nutr. 7 (2019) 1113–1122, http://dx.doi.org/10.1002/fsn3.956.

[75] S. Taheri, et al., Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial, Lancet Diabetes Endocrinol. 8 (6) (2020) 477–489, http://dx.doi.org/10.1016/S2213-8587(20)30117-0.

[76] C. Guidone, M. Manco, E. Valera-Mora, Iaconelli A., D. Gniuli, A. Mari, G. Nanni, M. Castagneto, M. Calvani, G. Mingrone, Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery, Diabetes 55 (7) (2006) 2025–2031, http://dx.doi.org/10.2337/db06-0068.

[77] S. Steven, K.G. Hollingsworth, P.K. Small, S.A. Woodcock, A. Pucci, B. Aribisala, A. Al-Mrabeh, R.L. Batterham, R. Taylor, Calorie restriction and not glucagon-like peptide-1 explains the acute improvement in glucose control after gastric bypass in type 2 diabetes, Diabetic Med. 33 (12) (2016) 1723–1731, http://dx.doi.org/10.1111/dme.13257.

[78] S. Steven, K.G. Hollingsworth, P.K. Small, S.A. Woodcock, A. Pucci, B. Aribisala, A. Al-Mrabeh, A.K. Daly, R.L. Batterham, R. Taylor, Weight loss decreases excess pancreatic triacylglycerol specifically in type 2 diabetes, Diabetes Care 39 (2016) 158–165, http://dx.doi.org/10.2337/dc15-0750.

[79] R. Taylor, Etiology and reversibility, Diabetes Care 36 (2013) 1047–1055, http://dx.doi.org/10.2337/dc12-1805.

[80] K. Pinnick, M. Neville, A. Clark, B. Fielding, Reversibility of metabolic and morphological changes associated with chronic exposure of pancreatic islet $\beta$-cells to fatty acids, J. Cell. Biochem. 109 (2010) 683–692, http://dx.doi.org/10.1002/jcb.22445.

[81] B. Gaborit, I. Abdesselam, F. Kober, A. Jacquier, O. Ronsin, O. Emungania, N. Lesavre, M.-C. Alessi, J.C. Martin, M. Bernard, A. Dutour, Ectopic fat storage in the pancreas using H-MRS: importance of diabetic status and modulation with bariatric surgery induced weight loss, Int. J. Obes. 39 (2015) 480–487, http://dx.doi.org/10.1038/ijo.2014.126.

[82] K. Hall, et al., Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men, Am. J. Clin. Nutr. 104 (2) (2016) 324–333, http://dx.doi.org/10.3945/ajcn.116.133561.

[83] J.S. Volek, M.L. Fernandez, R.D. Feinman, S.D. Phinney, Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome, Prog. Lipid Res. 47 (5) (2008) 307–318, http://dx.doi.org/10.1016/j.plipres.2008.02.003.

[84] S.D. Phinney, B.R. Bistrian, R.R. Wolfe, G.L. Blackburn, The human metabolic response to chronic ketosis without calorie restriction: physical and biochemical adaptation, Metabolism 32 (8) (1983) 757–768, http://dx.doi.org/10.1016/0026-0495(83)90105-1.

[85] S.D. Phinney, E. Danforth, B.M. Lagrange, Capacity for moderate exercise in obese subjects after adaptation to a hypocaloric, ketogenic diet, J. Clin. Invest. 66 (5) (1980) 1152–1161, http://dx.doi.org/10.1172/JCI109945.

[86] A.J. Nordmann, A. Nordmann, M. Briel, U. Keller, W.S. Yancy, B.J. Brehm, H.C. Bucher, Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: A meta-analysis of randomized controlled trials, Arch. Intern. Med. 166 (3) (2006) 285–293, http://dx.doi.org/10.1001/archinte.166.3.285.

[87] M. Hession, C. Rolland, U. Kulkarni, A. Wise, J. Broom, Systematic review of randomized controlled trials of low-carbohydrate vs low-fat/low-calorie diets in the management of obesity and its comorbidities, Obes. Rev. 10 (2008) 36–50, http://dx.doi.org/10.1111/j.1467-789X.2008.00518.x.

[88] M.J. Sharman, W.J. Kraemer, D.M. Love, N.G. Avery, A.L. Gómez, T.P. Scheett, J.S. Volek, A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men, Am. College Sports Med. 33 (S213) (2002) 1879–1885, http://dx.doi.org/10.1093/jn/132.7.1879.

[89] W.S. Yancy, M.K. Olsen, J.R. Guyton, R.P. Bakst, E.C. Westman, A low-carbohydrate ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: A randomized controlled trial, Ann. Intern. Med. 140 (2004) 769–777, http://dx.doi.org/10.7326/0003-4819-140-10-200405180-00006.

[90] C.A. Thomson, A.T. Stopeck, J.W. Bea, E. Cussler, E. Nardi, G. Frey, P.A. Thompson, Changes in body weight and metabolic indexes in overweight breast cancer survivors enrolled in a randomized trial of low-fat versus reduced carbohydrate diets, Nutrition and Cancer 62 (8) (2010) 1142–1152, http://dx.doi.org/10.1080/01635581.2010.513803.

[91] E.J. Parks, M.K. Hellerstein, Carbohydrate-induced hypertriacylglycerolemia: historical perspective and review of biological mechanisms, Am. J. Clin. Nutr. 71 (2) (2000) 412–433, http://dx.doi.org/10.1093/ajcn/71.2.412.

[92] M. Chumakova-Orin, C. Vanetta, D.P. Moris, A.D. Guerron, Diabetes remission after bariatric surgery, World J. Diabetes 12 (7) (2021) 1093–1101, http://dx.doi.org/10.4239/wjd.v12.i7.1093.

[93] J. Zhu, R. Gupta, M. Safwa, The mechanism of metabolic surgery: Gastric center hypothesis, Obes. Surg. 26 (7) (2016) 1639–1641, http://dx.doi.org/10.1007/s11695-016-2175-3.

[94] R. Taylor, R.R. Holman, Normal weight individuals who develop type 2 diabetes: the personal fat threshold, Clin. Sci. (Lond) 128 (7) (2015) 405–410, http://dx.doi.org/10.1042/CS20140553.

[95] Y. Zhou, L. Rui, Leptin signaling and leptin resistance, Front. Med. 7 (2) (2013) 207–222, http://dx.doi.org/10.1056/NEJM200105033441801.

[96] W. Kopp, Diet-induced hyperinsulinemia as a key factor in the etiology of both benign prostatic hyperplasia and essential hypertension? Nutr. Metab. Insights 11 (2018) 1–11, http://dx.doi.org/10.1177/1178638818773072.

[97] G. Schofield, G. Henderson, S. Thornley, C. Crofts, Very low-carbohydrate diets in the management of diabetes revisited, NZMJ 129 (1432) (2016) 67–74, https://pubmed.ncbi.nlm.nih.gov/27356254/.

[98] F.F. Samaha, et al., A low-carbohydrate as compared with a low-fat diet in severe obesity, N. Engl. J. Med. 348 (2003) 2074–2081, http://dx.doi.org/10.1056/NEJMoa022637.

[99] M.D. Gadgil, L.J. Appel, E. Yeung, C.A.M. Anderson, F.M. Sacks, E.R. Miller, The effects of carbohydrate, unsaturated fat, and protein intake on measures of insulin sensitivity, Diabetes Care 36 (5) (2013) 1132–1137, http://dx.doi.org/10.2337/dc12-0869.

[100] J.K. Kirk, D.E. Graves, T.E. Craven, E.W. Lipkin, M. Austin, K.L. Margolis, Restricted-carbohydrate diets in patients with type 2 diabetes: A meta-analysis, J. Am. Diet. Assoc. 108 (1) (2013) 91–100, http://dx.doi.org/10.1016/j.jada.2007.10.003.

[101] G.I. Shulman, Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease, N. Engl. J. Med. 371 (12) (2014) 1131–1141, http://dx.doi.org/10.1056/NEJMra1011035.

[102] C.S. Mantzoros, F. Magkos, M. Brinkoetter, E. Sienkiewicz, T.A. Dardeno, S.-Y. Kim, O.-P.R. Hamnvik, A. Koniaris, Leptin in human physiology and pathophysiology, Am. J. Physiol. Endocrinol. Metab. 301 (4) (2011) E567–E584, http://dx.doi.org/10.1152/ajpendo.00315.2011.

[103] R.B. Harris, Direct and indirect effects of leptin on adipocyte metabolism, Biochim. Biophys. Acta 1842 (4) (2014) 414–423, http://dx.doi.org/10.1016/j.bbadis.2013.05.009.

[104] W.A. Banks, A.B. Coon, S.M. Robinson, A. Moinuddin, J.M. Shultz, R. Nakaoke, J.E. Morley, Triglycerides induce leptin resistance at the blood–brain barrier, Diabetes 53 (5) (2004) 1253–1260, http://dx.doi.org/10.2337/diabetes.53.5.1253.

[105] J. Friedman, Obesity in the new millenium, Nature 404 (6778) (2000) 632–634, http://dx.doi.org/10.1038/35007504.

[106] M.G. Myers, S.B. Heymsfield, C. Haft, B.B. Kahn, M. Laughlin, R.L. Leibel, M.H. Tschop, J.A. Yanovski, Defining clinical leptin resistance - challenges and opportunities, Cell Metab. 15 (2) (2012) 150–156, http://dx.doi.org/10.1016/j.cmet.2012.01.002.

[107] K. Mendoza-Herrera, A.A. Florio, M. Moore, A. Marrero, M. Tamez, S.N. Bhupathiraju, J. Mattei, The leptin system and diet: A mini review of the current evidence, Front. Endocrinol. 12 (2021) 749050, http://dx.doi.org/10.3389/fendo.2021.749050.

[108] A. Tremblay, F. Dutheil, V. Drapeau, L. Metz, B. Lesour, R. Chapier, B. Pereira, J. Verney, J.S. Baker, A. Vinet, G. Walther, P Obert, D. Courteix, D. Thivel, Long-term effects of high intensity resistance and endurance exercise on plasma leptin and ghrelin in overweight individuals: the resolve study, Appl. Physiol. Nutr. Metab. 44 (11) (2019) 1172–1179, http://dx.doi.org/10.1139/apnm-2019-0019.

[109] S. Blüher, G. Panagiotou, P. Petroff, J. Markert, A. Wagner, T. Klemm, A. Filippaios, A. Keller, C.M. Mantzoros, Effects of a 1-year exercise and lifestyle intervention on irisin, adipokines, and inflammatory markers in obese children, Obesity 22 (7) (2014) 1701–1708, http://dx.doi.org/10.1002/oby.20739.

[110] K.A. Krawczewski Carhuatanta, G. Demuro, M.H. Tschöp, P.T. Pfluger, S.C. Benoit, S. Obici, Voluntary exercise improves high-fat diet-induced leptin resistance independent of adiposity, Endocrinology 152 (7) (2011) 2655–2664, http://dx.doi.org/10.1210/en.2010-1340.

[111] Q. Dong, F. Giorgianni, X. Deng, S. Beranova-Giorgianni, D. Bridges, E.A. Park, R. Raghow, M.B. Elam, Phosphorylation of sterol regulatory element binding protein-1a by protein kinase a (PKA) regulates transcriptional activity, Biochem. Biophys. Res. Commun. 449 (4) (2014) 449–454, http://dx.doi.org/10.1016/j.bbrc.2014.05.046.

[112] F. Ameer, S. Scandiuzzi, S. Hasnain, H. Kalbacher, N. Zaidi, De novo lipogenesis in health and disease, Metabolism 63 (7) (2014) 895–902, http://dx.doi.org/10.1016/j.metabol.2014.04.003.

[113] K.N. Frayn, Metabolic Regulation: A Human Perspective, third ed., Wiley-Blackwell, 2010.

[114] L.R. Peterson, P. Herrero, J. McGill, K.B. Schechtman, Z. Kisrieva-Ware, D. Lesniak, R.J. Gropler, Fatty acids and insulin modulate myocardial substrate metabolism in humans with type 1 diabetes, Diabetes 57 (1) (2008) 32–40, http://dx.doi.org/10.2337/db07-1199.

[115] C.C. Chow, K. Hall, The dynamics of human body weight change, PLoS Comput. Biol. 4 (3) (2008) e1000045, http://dx.doi.org/10.1371/journal.pcbi.1000045.