Author:
Garbutt, James D W

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Dietary patterns and progression of Type 2 Diabetes

Dietary Patterns and the Progression of Type 2 Diabetes

James Garbutt

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Abstract

Background: Glycaemic control in type 2 diabetes (T2DM) deteriorates progressively over time. Diet is a cornerstone of T2DM management. It is unknown if dietary patterns impact glycaemia independent of weight change or if they impact rates of long-term glycaemic deterioration. Also unknown is whether short- and long-term dietary pattern changes differ between men and women following non-prescriptive dietetic advice.

Methods: In people recently-diagnosed with T2DM, a 'carb/fat balance' dietary pattern and an 'obesogenic' dietary pattern were derived using reduced-rank regression, based on hypothesised nutrient-mediated pathways linking diet with glycaemia directly or indirectly via bodyweight. Study 1 explored weight-independent associations between changes in dietary patterns and changes in glycaemic control during a 12-month non-prescriptive dietary intervention. Study 2 explored whether differences existed between men and women in short- and long-term 'obesogenic' dietary pattern change during (<12 months) or following this dietary intervention (1-6 years). Study 3 explored associations between 'carb/fat balance' dietary patterns and the rate of glycaemic deterioration during the 5-year follow-up. Study 4 replicated analyses from study 3 in a larger, more diverse, purely observational cohort.

Results: Increases in standardised 'carb/fat balance' dietary pattern scores, shifting total intakes of carbohydrates higher and fats lower, associated with short-term reductions in HbA1c independent of weight loss (β=-1.54 [95%CI: -2.96, -0.13] mmol/mol/SD). No associations were found linking this dietary pattern to rates of long-term glycaemic deterioration. Study 2 found no differences in how dietary patterns change between men and women over the short- or long-term following typical non-prescriptive dietetic advice.

Conclusions: Dietary interventions in T2DM require no further tailoring to sex. Dietary patterns moving carbohydrate and fat intakes closer to meeting UK healthy eating guidelines provide small, short-term, weight loss-independent benefits to glycaemic control. Dietary patterns do not impact glycaemic progression over the long-term. Weight loss should remain the primary focus of T2DM dietary management.

299 words

Dedication and Acknowledgements

I would like to thank everyone who has supported me in completing this PhD. Without the assistance, encouragement and friendship of the following people, it would not have been possible.

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Author’s declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ..... DATE:.....

Publications arising from this thesis

Original research articles

Garbutt J, England C, Jones AG, Andrews RC, Salway R and Johnson L. Is glycaemic control associated with dietary patterns independent of weight change in people newly diagnosed with type 2 diabetes? Prospective analysis of the Early-ACTivity-In-Diabetes trial. BMC Medicine. 2022; 20:161. DOI: 10.1186/s12916-022-02358-5.

Author contributions: JG had full access to all data in the study and takes responsibility for the accuracy of the data analysis. All authors made substantial contributions to the conception and design of the study and analysis and interpretation of data. JG entered data and planned and conducted the analysis. CE and LJ supervised the data entry and analysis. RA was responsible for designing the study, recruiting the patients and collecting the data. JG wrote the first draft of the article and revised it in response to comments; LJ, CE, RS, RA and AJ reviewed and edited the manuscript and contributed to discussion. All authors read and approved the final manuscript.

Datasets

Garbutt J. Early-ACTID dietary pattern data. DataBris. 2021. https://doi.org/10.5523/bris.3o7bip8v2ae8m2gdfpu1pt5rlz.

Conference proceedings

Garbutt JDW, England C, Papadaki A, Andrews RC, Jones AG, and Johnson L. P156: Is adherence to a Mediterranean diet associated with progression of Type 2 diabetes? Diabetic Medicine. 2018; 35(1):85.

- Poster presentation at Diabetes UK Professional conference, March 2018

Garbutt JDW, England C, Andrews RC, Jones AG, Johnson L. P55: Are changes in a low-carbohydrate, high-fat diet pattern associated with subsequent changes in HbA1c during an intensive diet and physical activity intervention? Diabetic Medicine. 2020; 37(1):44.

- Poster presentation at Diabetes UK Professional conference, March 2020 (cancelled due to COVID-19)

Further information on author contributions to data preparation: JG coded n=49 diet diaries returned by Early-ACTID participants at the 12-month timepoint, checked accuracy of remaining n=254 pre-coded 12-month diet diaries, and coded all diet diaries returned at the 3- and 6-year timepoints (n=137 and n=197 respectively). JG manually assigned all individual food and drinks reported by Early-ACTID participants (n=1,924 items) to separate food groups for use in deriving each dietary pattern explored in this thesis (n=65 food groups for the 'carb/fat balance' dietary pattern and n=47 food groups for the 'obesogenic' dietary pattern). JG also manually assigned all individual food and drinks reported by DIRECT 2.2 participants (n=2,049 items) to n=65 food groups for use in deriving a 'carb/fat balance' dietary pattern. All analyses of DIRECT 2.2 data were conducted remotely on a secure Linux server.

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Abbreviations

ADOPT - A Diabetes Outcome Progression Trial

AHEI - Alternate Healthy Eating Index

aHR - adjusted hazard ratio

AIC - Aikake information criterion

BIC - Bayesian information criterion

BMI - body mass index

CC - congruence coefficient

CHD - coronary heart disease

CHO - carbohydrate

CI - confidence interval

CoF - coefficient of failure

COFID - Composition of Foods Integrated Dataset

cpm - counts per minute

CRP - C-Reactive Protein

CVD - cardiovascular disease

DASH - Dietary-Approaches-to-Stop-Hypertension

DED - dietary energy density

DESMOND - Diabetes Education and Self Management for Ongoing and Newly Diagnosed

DiRECT - Diabetes Remission Clinical Trial

DIRECT - Diabetes Research on Patient Stratification (study)

DLW - doubly labelled water

DPP4 - dipeptidyl peptidase-4 (inhibitor)

Early-ACTID - Early ACTivity-In-Diabetes (trial)

EASD - European Association for the Study of Diabetes

EER - estimated energy requirement

EPIC - European Prospective Investigation into Cancer and Nutrition

EVOO - extra-virgin olive oil

FFQ - food frequency questionnaire

FPG - fasting plasma glucose

GAD - glutamic acid decarboxylase

GI - glycaemic index

GL - glycaemic load

GLP1 - glucagon-like peptide-1

GODARTS - Genetics of Diabetes Audit and Research in Tayside Study

HDL - high-density lipoprotein

HEI - Healthy Eating Index

HOMA2-%B - homeostasis model assessment 2 of beta-cell function

HOMA2-IR - homeostasis model assessment 2 of insulin resistance

HOMA2-IS - homeostasis model assessment 2 of insulin sensitivity

hpfVM - high-pass-filtered vector magnitude

HPLC - High performance liquid chromatography

HR - hazard ratio

IA-2 - islet antigen-2

ICC - intraclass correlation coefficient

IMD - Index of Multiple Deprivation

INTERMAP - International Collaborative of Macronutrients, Micronutrients and Blood Pressure

LDL - low-density lipoprotein

MAR – missing at random

MCAR - missing completely at random

MD - mean difference

MUFA - monounsaturated fatty acids

MVPA - moderate-vigorous physical activity

NDNS - National diet and Nutrition Survey

NICE - National Institute of Health and Care Excellence

OHA - oral hypoglycaemic agent

OR - odds ratio

PAL - physical activity level

PCA - principal component analysis

PPG - post-prandial glucose

PREDIMED - Prevención con Dieta Mediterránea (trial)

PUFA - polyunsaturated fatty acids

Q1 - quartile 1

Q3 – quartile 3

RCT - randomised controlled trial

rEI - reported energy intake

RR - relative risk

RRR - reduced-rank regression

SCFA - short-chain fatty acids

SD - standard deviation

SFA - saturated fatty acids

SGLT2 - sodium-glucose co-transporter-2 (inhibitor)

SOS - Swedish Obese Subjects (study)

SSB - sugar-sweetened beverage

T2DM - type 2 diabetes mellitus

TEI - Total energy intake.

UKPDS - UK Prospective Diabetes Study

VLED - very-low energy diets

Chapter 1 - Introduction

1.1 Type 2 diabetes

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterised by resistance to insulin action combined with defects in pancreatic beta-cell function, manifesting clinically through chronic, high blood glucose levels [1]. It is a disease with high rates of morbidity and mortality [2], placing an individual at a two-fold increased risk of (duration-dependent) microvascular and macrovascular complications, independently of commonly coexisting conditions such as hypertension and dyslipidaemia [3, 4].

Worldwide combined diabetes prevalence for adults between 20 and 79 years of age was estimated at 537 million in 2021; approximately 4 million of whom reside within the UK [5]. Pooled data from population-level studies reveal total global adult diabetes trends increasing from 180 million in 1980 to 422 million in 2014 [6]; a prevalence increase for both sexes from 4.7% to 8.5%, even after taking into account changing diagnostic criteria (see section 2.1) over time. Such trends also mirror the global increases in overweight and obesity [7], with around 80-90% of people T2DM being overweight [8, 9]. Ethnic disparities in T2DM also exist, with South Asian and Black people found to be two- to four-fold more likely to develop T2M compared with White people [10].

T2DM makes up approximately 90% of diabetes cases within the UK, although similar percentages are observed globally [5, 11]. Direct and indirect T2DM-related costs to both the NHS and UK society were estimated to be over £21.7 billion in 2010/2011, with projections indicating this cost will rise to over £35.6 billion by 2035/2036 [12]. T2DM's increasing worldwide prevalence, deleterious impact on quality of life [13, 14] and financial burdening of healthcare services, renders finding improvements to both preventative and management strategies a leading societal concern.

1.2 Type 2 diabetes progression and the role of dietary patterns

T2DM is considered a progressive disease [15]. For the majority of people with T2DM, pancreatic beta-cell function and insulin sensitivity continues to decline over time, leading to progressively increasing average blood glucose despite escalating use of glucose-lowering medications [15–17]. However, the rate at which T2DM progresses is found to be highly variable amongst individuals [15,

18]; reasons for which are not yet understood [19]. Lifestyle-related factors such as diet have been studied fairly extensively for their effects on short-term glycaemic control in T2DM [20, 21], and weight loss is consistently linked with improvements in glycaemia [22]. However, the specific effects of diet on longer-term deterioration of glycaemia in T2DM, in the context of a progressing disease state, remains relatively unexplored.

Diet is a fundamental part of T2DM management, with current guidelines emphasising improving diet quality as a whole, recommending healthful dietary patterns rather than specific macronutrient or food intakes [20, 23]. Individual macronutrients have been shown to exert differing effects on glycaemia, pancreatic beta-cell function and also insulin sensitivity [24–27], yet trials involving people with T2DM have produced conflicting results for determining the most appropriate intakes [28]. Separating effects of dietary composition change on glycaemia from the known effects of weight change is however difficult as both typically co-occur. Acknowledging that people do not eat individual nutrients or foods in isolation, a dietary pattern is a multidimensional construct reflecting real-world, habitual eating behaviours, capturing combined consumption of multiple nutrients and foods simultaneously. Data-driven statistical techniques like reduced-rank regression [29], used throughout this thesis (see section 2.6.1.3.1 for further details), can derive dietary patterns that capture the specific variation in combined nutrient intakes thought to be causally related to disease. This could be of key importance for identifying mechanisms of action of diet on diseases with multifactorial aetiologies, such as T2DM.

Dietetic practice in the UK typically adopts a non-prescriptive, patient-centred approach [30], whereby proposed dietary changes are decided on by the patient based on what they are willing and feel able to make. However, evidence is scarce for how dietary patterns change in people with T2DM following such an intervention. Importantly, the dietary patterns of men and women are typically found to differ in the UK and globally [31, 32], potentially as a result of differences in both biology as well as behavioural differences related to gender social norms [33, 34]. These differences in behavioural norms have the potential to impact the short- and long-term dietary pattern changes seen under a non-prescriptive approach. Thus, to maximise dietary pattern change in both sexes, a dimorphic approach may be required.

This thesis aims to explore associations between dietary patterns and changes in glycaemia over both the short-term (glycaemic control independent of weight change) and long-term (rates of glycaemic deterioration) in early type 2 diabetes. The dietary patterns will be derived to act mechanistically through disease-relevant nutrient intakes informed by current evidence. In line with

this, this thesis also aims to explore whether dietary patterns change similarly for both men and women over both the short- and long-term under a standard, non-prescriptive approach.

1.3 Research questions

The research questions to be explored in this PhD thesis are as follows:

1) Do changes in nutrient-mediated dietary patterns associate with short-term glycaemic control independent of the effects of weight change in early type 2 diabetes?
2) During and following a non-prescriptive, patient-centred dietary intervention in early type 2 diabetes, do dietary pattern changes diverge between men and women?
3) Do nutrient-mediated dietary patterns associate with longer-term glycaemic progression in early type 2 diabetes?
4) Are associations between nutrient-mediated dietary patterns and longer-term glycaemic progression in early type 2 diabetes replicable and generalisable between cohorts?

These will be explored across four studies, as outlined in Table 1.1.

1.4 Structure of the thesis

An overview of the structure of this thesis is presented in Figure 1.1 and Table 1.1.

Figure 1.1: Thesis study overview.

Study 1 aims to explore whether changes in nutrient-mediated dietary patterns associate with changes in glycaemic control during a 12-month, non-prescriptive, patient-centred dietary intervention in early type 2 diabetes, independent of effects relating to weight changes. Study 2 aims to explores whether changes made in dietary patterns following the dietary intervention diverges between men and women over both the short- and long-term. Study 3 aims to explore whether dietary patterns associate with the rate of long-term glycaemic deterioration during 5-year follow-up of the dietary intervention. Study 4 aims to explore whether dietary patterns associate with the rate of glycaemic deterioration in a larger cohort with greater geographical diversity who received no trial intervention.

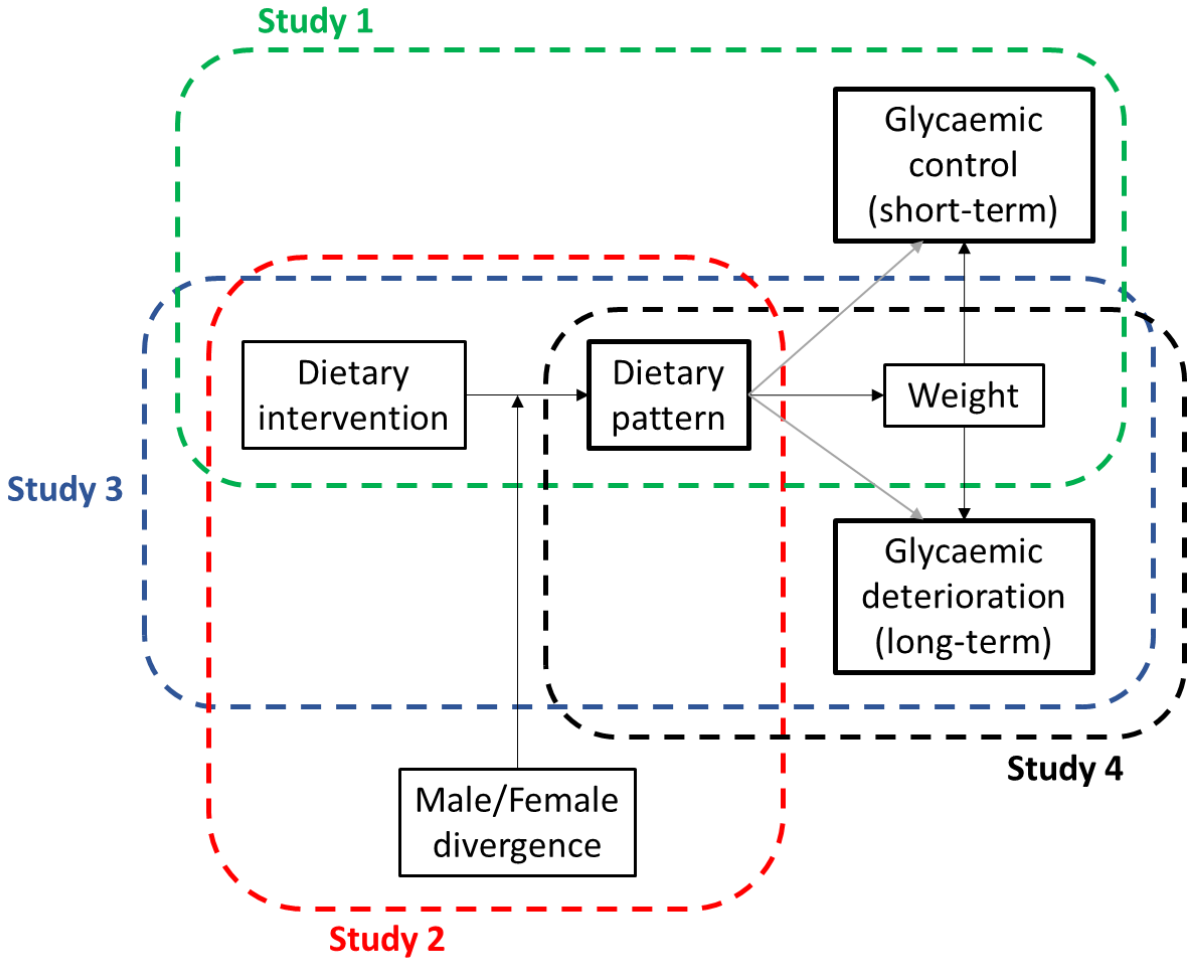


Table 1.1: Overview of thesis structure.

Thesis chapter	Summary	Research question
Chapter 2: Background, Methods and Literature review	An overview of literature relevant to the thesis	
Chapter 3: Study 1 - Nutrient-mediated, data-driven dietary patterns and glycaemic control	This chapter details a secondary analysis of data from the 12-month Early-ACTivity-In-Diabetes (Early-ACTID) randomised controlled trial that provided a non-prescriptive dietary intervention, with or without physical activity advice, in early type 2 diabetes. Dietary patterns theorised to relate with glycaemia directly or indirectly via weight loss are derived using reduced-rank regression from four-day food diary data. Changes in dietary patterns are explored for association with changes in glycaemic control, independently of effects of bodyweight change. The study assesses relationships between nutrient-mediated dietary patterns and shorter-term glycaemic changes mostly attributable to lifestyle rather than a progression of disease.	1
Chapter 4: Study 2 - Differences in dietary pattern change between men and women following a non-prescriptive, patient-centred dietary intervention	This chapter details a secondary analysis of dietary data from the 12-month Early-ACTID trial and it's 5-year follow-up, exploring whether dietary pattern changes diverged between men and women during and after the non-prescriptive dietary intervention. This study assesses the possibility that men and women require a dimorphic approach to achieve dietary pattern change in type 2 diabetes.	2
Chapter 5: Study 3 - Dietary patterns and glycaemic deterioration following the Early-ACTID trial	This chapter details a secondary analysis of data from the 12-month Early-ACTID trial and its 5 year follow-up, exploring associations between nutrient-mediated dietary patterns and rates of long-term glycaemic deterioration. The study assesses relationships between nutrient-mediated dietary patterns and longer-term glycaemic changes attributable, at least in part, to progression of disease.	3

Chapter 6: Study 4 - Dietary patterns and glycaemic deterioration in the DIRECT 2.2 observational study	This chapter details an analysis of observational data from people with recently-diagnosed type 2 diabetes taking part in the 36-month Diabetes Research on Patient Stratification (DIRECT) 2.2 cohort study. This study aimed to replicate analyses presented in Chapter 5 but in a larger sample with greater geographical diversity and where participants had received no prior trial intervention. The study again assesses relationships between nutrient-mediated dietary patterns and longer-term glycaemic changes attributable, at least in part, to progression of disease.	3, 4
Chapter 7: Discussion	Overall discussion and conclusion	

Chapter 2 - Background, Methods and Literature Review

The background, methods and literature relevant to this thesis are reviewed in this chapter.

2.1 Diagnosis of type 2 diabetes and glycated haemoglobin (HbA1c)

A formal diagnosis of type 2 diabetes (T2DM) is given under any of the following [1, 35]:

- Fasting plasma glucose (FPG) ≥7.0 mmol/L.
- 2-hour plasma glucose following a 75g oral glucose load (oral glucose tolerance test) ≥11.1 mmol/L.
- Glycated haemoglobin (HbA1c) ≥48 mmol/mol (6.5%).

The above diagnostic thresholds are also used for other forms of diabetes such as type 1 and monogenic diabetes, diseases of the exocrine pancreas (such as cystic fibrosis), or drug- or chemical-induced diabetes (such as following organ-transplantation) [23]. Tests are repeated to confirm a correct reading before formal diagnosis.

HbA1c is a weighted 'average' measure of blood glucose levels over the preceding three-month period (unless contraindicated by conditions affecting red blood cell turnover), representing the degree of glycation of haemoglobin in red blood cells [36]. Both FPG and post-prandial glucose (PPG) contribute to HbA1c concentrations, and although variation between mean glucose levels and HbA1c measures have been demonstrated between individuals, the two are considered to generally correlate well over time [23, 37]. Additionally, HbA1c is a consistent metric of glycaemia for predicting T2DM complication risk [37, 38], with one meta-analysis of 26 cohort studies calculating a 17% greater risk of cardiovascular disease for every 1% increase in HbA1c [39].

People on course to develop T2DM will initially pass through a 'pre-diabetic' stage. During this time, blood glucose markers are increased above normal (HbA1c 42-47 mmol/mol (6.0-6.5%)) but do not yet meet the criteria for T2DM diagnosis [40, 41]. However, disproportionate risk of cardiovascular complications, such as retinopathy, exist for glycaemic measures even slightly above normal [35]. Prevention of T2DM is itself important but all studies contained in this thesis concern people who have already received a T2DM diagnosis.

2.2 Pathology of type 2 diabetes

In normal health, rising blood glucose stimulates the secretion of insulin from the beta-cells of the pancreas through induced changes in beta-cell membrane potential. This causes a pulsatile, oscillating pattern of insulin secretion that occurs in two phases [42]. 'First-phase' insulin response is an acute, rapid release of insulin lasting approximately ten minutes post-prandially, whilst the 'second-phase' insulin response is a slower, sustained release of insulin that lasts until glycaemic levels return to normal (4-7 mmol/L) [26]. Independently to glucose-induced effects, beta-cell insulin secretion can also be stimulated by incretin hormones, beta-adrenergic agonists, fatty acids and mono-basic amino acids (see sections 2.7.1.2 and 2.7.1.3).

The maintenance of normoglycemia is determined by the balance between peripheral insulin sensitivity and insulin secretion, with insulin secretion increasing when insulin sensitivity is reduced; as is the case in conditions of chronic energy surplus [43, 44]. However, when blood glucose levels are raised for prolonged periods, the chronic requirement of increased insulin secretion eventually leads to a deterioration in beta-cell insulin secretory capacity [45]. What follows is a progressive reduction in beta-cell mass and number [46, 47] and a gradual loss of the first-phase insulin response [15]. With sufficient beta-cell deterioration, insulin secretion no longer matches the level required to overcome insulin resistance and glycaemia crosses the diagnostic threshold for T2DM.

There are several potential mechanisms through which beta-cell function is thought to deteriorate in T2DM. These include effects of islet amyloid polypeptide (IAPP) aggregation, lipotoxicity and glucotoxicity, each triggering stress pathways including mitochondrial/oxidative and endoplasmic reticulum (ER) stress, inflammation and disrupted cellular protein clearance, with each individual pathway potentially acting synergistically to compound beta-cell loss [45].

Insulin and IAPP are co-expressed from the pancreatic beta-cells. When more insulin is required to be secreted to overcome reductions in insulin senstivity, more IAPP will also be produced. However, high secretion of IAPP can form oligomers that contribute to ER stress [48, 49], and have been observed to accumulate into insoluble fibrils in islets of people with T2DM, leading to beta-cell death [50, 51].

In the context of overweight and obesity, commonly co-occurring in people with T2DM [8, 9], beta-cells are typically exposed to higher than normal plasma lipid concentrations and greater ectopic storage of excess lipids [52]. This has a deleterious effect on beta-cell function and survival due to an

ensuing accumulation of toxic metabolic derivatives [53] (see also section 2.7.1.2). Energy over-consumption leads to further ectopic fat accumulation in the liver and skeletal muscle, triggering metabolic pathways that promote further insulin resistance and dyslipidaemia [44]. Although it is currently unclear to what extent or type of lipids beta-cells are predominantly exposed to in T2DM [45], remission of T2DM through substantial weight loss (see section 2.3.2.1) can be explained by the clearance of lipid from within the pancreas, promoting a reversal of beta-cell dysfunction and a return of the first-phase insulin response [54, 55].

Separately, chronic exposure to hyperglycaemia can itself exacerbate functional deterioration of beta-cells [56]. *In vitro* evidence indicates that high glucose exposure induces ER stress in human beta-cells, eventually triggering beta-cell death [57–60]. Furthermore, in human trials, restoration of beta-cell function has been achieved with intensive short-term (~2 weeks) insulin therapy early in the T2DM disease course, potentially durable for periods up to 1 year despite subsequent insulin therapy withdrawal [61, 62]. The exact mechanisms through which remediation of glucotoxicity leads to sustained improvement in beta-cell function is currently unclear [43], but is potentially related to re-differentiation of de-differentiated beta-cells following the instigation of short-term metabolic rest [48].

2.3 Current treatment of type 2 diabetes

Treatment of T2DM commonly involves a combination of pharmaceutical and lifestyle interventions. In line with best practise for modern healthcare [30, 63], guidelines recommend an individualised, patient-centred approach to T2DM care [4, 64], whereby the preferences, values and circumstances of the patient are accounted for during treatment.

2.3.1 Pharmaceutical intervention

Pharmaceutical management of glycaemia include oral hypoglycaemic medications (OHAs) and injectable therapies such as glucagon-like peptide-1 (GLP-1) agonists, and eventually, exogenous insulin. The major OHAs are biguanides (metformin), sulfonylureas, alpha-glucosidase inhibitors (acarbose), thiazolidinediones (‘glitazones’), dipeptidyl peptidase-4 (DPP-4) inhibitors (‘gliptins’) and sodium–glucose cotransporter-2 (SGLT-2) inhibitors (‘flozins’). Each work to control blood glucose through a variety of physiological mechanisms; either reducing insulin resistance and/or

gluconeogenesis, increasing insulin secretion by the pancreas, slowing carbohydrate digestion/absorption, or promoting glucosuria. Pharmaceutical prescriptions are personalised and based on drug effectiveness, presence of comorbidities, risks of hypoglycaemia, their effects on weight, side effects, costs, and patient preferences [4].

Medications are typically introduced in combination sequentially. The biguanide, metformin, is typically initiated for adults with T2DM at diagnosis as 'first-line' treatment, with dose increases and additional OHA medications being prescribed upon sufficient deterioration of HbA1c following standard protocols [4]. A meta-analysis of studies >3 months in length looking at comparative OHA effectiveness, indicated that each new class of OHA medication added to initial metformin therapy typically lowers HbA1c by approximately 7.7-12 mmol/mol (0.7–1.1%) [65]. Insulin is initiated once non-insulin therapies fail. Approximately 25% of patients with T2DM move on to insulin treatment by 6 years of initiating pharmacotherapy, increasing to 42% of patients after 10 years [66]. Polypharmacy with anti-hypertensives, antiplatelet therapy and lipid-lowering medications is also common for management of coexisting conditions of hypertension and dyslipidaemia.

2.3.2 Lifestyle interventions

2.3.2.1 Weight loss

Sustained weight loss through achieving an energy deficit is multilaterally advocated as one of the primary nutritional management strategies for overweight or obese adults with T2DM [4, 20, 21]. Weight loss is shown to improve HbA1c, insulin sensitivity, medication requirements, blood lipids, blood pressure and hence CVD risk in people with T2DM [22, 67]. Improvements appear proportional to the magnitude of weight lost. In a model of weight-loss RCT outcomes in T2DM by Gummesson et al [68], each kg of weight lost associated at group-level with a mean HbA1c reduction of 1.1 mmol/mol (0.1%). Improvements in HbA1c following weight loss also appear proportional to its initial value, with higher baseline HbA1c concentrations reducing to a greater degree under equivalent weight loss [68]. Guidelines recommend weight loss >5% initial bodyweight [20], although evidence for clinically relevant improvements in HbA1c (typically considered a reductions of 3.3 mmol/mol (0.3%) [69]) have been observed with as little as 2-5% weight loss [67].

The 12-month Diabetes Remission Clinical Trial (DiRECT) explored whether marked weight loss could instigate a 'remission' of T2DM; defined as HbA1c <48 mmol/mol (<6.5%) and ≥2 months without taking blood glucose-lowering medications [70]. Intervention participants (n=149) followed a liquid,

very-low energy (823-853 kcal/day) diet (VLED) for 3-5 months, followed by 2-8 weeks of stepped food reintroduction (approximately 50% carbohydrate, 35% total fat, 15% protein) alongside structured weight maintenance support. Results showed that remission status was achieved in 86%, 57%, and 34% of participants who lost ≥15kg, 10-15kg and 5-10kg respectively, indicating remission rates increased with greater weight loss. In turn, sustained remission at 24-months depended on the ability to maintain this weight loss [71]. However, a duration of disease >6 years appears to significantly reduce the ability of the beta-cells to reproduce the 'first-phase insulin response' and hence achieve disease remission [55, 72]. T2DM thus appears to progress to a 'point of no return', after which physiological damage of pancreatic beta-cells becomes irreversible.

Ongoing pilot studies within the UK are exploring the feasibility of DiRECT's VLED intervention within routine clinical practise [73]. Nevertheless, it remains a fact that not all people with T2DM are able to achieve such marked weight loss via lifestyle change, and preventing subsequent weight regain, common under any weight loss regime, requires substantial effort [74, 75]. Bariatric surgery can result in dramatic weight loss and subsequent T2DM remission if performed early enough in the disease course [23, 76], but such treatments are expensive and logistically infeasible for the vast majority of people with T2DM given current NHS resources. There thus remains a need to identify dietary strategies that may help prevent or at least delay glycaemic deterioration in T2DM in ways potentially independent of weight change.

2.3.2.2 Physical activity interventions

Like the general population, adults with T2DM are encouraged to engage in either 150 minutes or more of moderate-to-vigorous intensity, 75 minutes vigorous-intensity or 75 minutes interval aerobic activity each week [23]. Additionally, 2–3 sessions per week of resistance training are recommended alongside reduced sedentary time [23]. A combination of both aerobic and resistance exercise has been shown to reduce HbA1c to a greater degree than each type of exercise separately [77–79]. Structured exercise interventions with a duration of at least 8 weeks have previously demonstrated average HbA1c reductions of 7.7 mmol/mol (0.7%) in people with T2DM, independent of changes in exercise intensity, volume or a person's BMI [80]. Aside from benefits on HbA1c, beneficial effects of aerobic and resistance exercise in people with T2DM include lowered blood pressure, triglycerides, and insulin resistance and increases in lean body mass [81–83].

2.3.2.3 Dietary interventions

Dietary advice for T2DM management centres around glycaemic control and minimising CVD risk. There is currently insufficient quality of evidence for specifying percentages of energy from carbohydrates, protein, or fats that optimise glycaemic control for all individuals with T2DM. A range of dietary approaches are thus considered suitable for T2DM management, with Diabetes UK promoting 'general healthy eating' in-line with NICE [4] and UK dietary guidelines [20], and naming Mediterranean, Dietary-Approaches-to-Stop-Hypertension (DASH)-style and plant-based dietary patterns as suitable for both management of glycaemia and reduction of CVD risk [20, 21]. Evidence for associations between diet and glycaemia is discussed in greater detail in section 2.7.

2.4 Progression of type 2 diabetes

Following diagnosis of T2DM, the disease course typically propagates via declining pancreatic beta-cell function and increasing insulin resistance, manifesting clinically via deteriorations in HbA1c, FPG, and PPG levels [15]. Although recovery of beta-cell function appears possible through substantial weight loss early in the disease course (see section 2.3.2.1) [70], and to some degree with early intensive insulin therapy over the short-term [61, 62], the pathophysiology is typically degenerative and decreasing efficacy of glucose-lowering medications renders long-term glycaemic management difficult to maintain [16, 17]. In this thesis, 'progression' of T2DM refers to this ongoing deterioration in the ability to maintain glycaemia despite escalating pharmaceutical intervention.

Individual rates of disease progression are highly variable [15, 18]; the aetiological reasons for which are not fully understood [19]. Over 400 genetic variants have been associated with T2DM development, but most are common and appear on aggregate to explain minimal phenotypic variation [19, 84, 85]. Efforts have been made to define 'subtypes' of T2DM through data-driven clustering methods based on clinical markers such as age, body mass index (BMI), HbA1c, homeostasis model assessment 2 estimates of beta-cell function (HOMA2-%B) and insulin sensitivity (HOMA2-IS) (see section 2.4.1.2) and presence or absence of glutamic acid decarboxylase (GAD) autoantibodies [86–88]. Testing positive for GAD autoantibodies indicates presence of an autoimmune process and is highly suggestive of type 1 diabetes rather than 'typical' type 2 diabetes [89]. Five sub-groups, reproduced in other cohorts [86–88], were shown to differ in respect to time to initiating medications and to complications [86]. However, assigning individuals to an aetiological cluster inherently leads to information loss when forced to assign individuals to one group versus

another [19, 90]. Importantly, such sub-group based stratification of individuals have failed to outperform the predictive ability of single clinical measures, such as age at diagnosis and baseline kidney function, for predicting later HbA1c changes and kidney disease respectively [90]. Hence, despite significant phenotypic heterogeneity existing in T2DM, there remains significant clinical utility in using basic measures to predict subsequent disease trajectories. Basic lifestyle-related factors such as diet or physical activity may also help explain at least some of the intrinsic variation in the observed rates of disease progression.

It should be noted that in the majority of current literature relating diet to glycaemia in T2DM (see section 2.7), diet is explored in regards to changes in glycaemic control over only short timescales (typically ≤12 months). This may be representative of glycaemic effects attributable to lifestyle change, but insufficient for assessing associations with longer-term glycaemic deterioration due to progression of disease state. It is therefore key to note that short-term changes in glycaemic control do not necessarily translate to changes in the rate of progressive, long-term glycaemic deterioration. Although rates of progression can indeed vary, as highlighted above, to truly assess disease progression and the variables which may predict or impact on it, research periods of the order of years are required.

2.4.1 Measuring type 2 diabetes progression

Type 2 diabetes progression can be assessed in various ways. These vary in how directly they assess pathophysiological progression and may be of more or less immediate interest to different benefactors (i.e. patients, clinicians or policy makers). The most direct methods involve assessment of long-term glycaemic measures such as HbA1c (alongside adjustment for effects of glucose-lowering medications), assessing beta-cell secretory function alongside insulin resistance, or assessing time to initiation of medication. The following sections explore these in further detail. Complication incidence could be a further progression marker of T2DM. However, complication risk is related to uncontrolled hyperglycaemia, dyslipidaemia and hypertension [3], and is thus a more indirect/distal marker compared to measures of glycaemia such as HbA1c. Due to the requirement for long follow-up times (developmental periods for T2DM complications can exceed 20 years [11]), assessing potential relationships between repeated diet measures and disease progression via complication incidence was deemed impractical in this thesis.

2.4.1.1 Time to medication initiation or escalation

The most common outcome measure for assessing T2DM progression in previous research has been the time to initiation or escalation of glucose-lowering medications [91] or otherwise reaching pre-specified glycaemic thresholds [92–98]. A notable trial by Esposito et al [97, 98] assessed the effects of a Mediterranean diet specifically on delaying the need for glucose-lowering medications and is discussed in section 2.7.3.1 rather than here.

The UK Prospective Diabetes Study (UKPDS) was a twenty-year randomised-controlled trial (RCT) involving 5,102 people newly-diagnosed with T2DM randomised to either conventional dietary advice (recommending 50% total energy intake (TEI) from carbohydrates, 30-35%TEI from fat and 30g/day fibre) or additional intensive glucose control (target FPG <6mmol/l) through metformin (if overweight), sulphonylurea or insulin treatment [99]. The UKPDS was one of the first studies to show the progressive loss of glycaemic control in T2DM despite escalating medication use [16]. Based on time to initiating insulin (in those not originally assigned to insulin) by 6 years, those testing positive for GAD and other auto-antibodies were more likely to progress to insulin (Odds Ratio (OR) for positive GAD in those ≥45 years of age: 5.62 [95%CI: 3.23, 9.80]) [100], as were those with lower baseline age (Relative Risk (RR): 1.69 [95%CI: 1.37, 2.09] relative to those aged ≥54 years) and beta-cell secretory function (RR: 2.38 [1.53, 3.69] for HOMA-%B <27.1% versus ≥55.1%) and those with higher baseline HbA1c (56% vs 26.4% participants requiring insulin with baseline HbA1c ≥8.6% vs <6.8% respectively) [101]. An observational analysis of primary care data by Pani, Nathan and Grant [93] used a dichotomous progression outcome, defined by either initiation of glucose-lowering medication or a HbA1c ≥7%, in participants with established T2DM. Out of 705 individuals, 200 'progressors' were identified over a 1-year follow-up period, with progressors again more likely to be younger (OR: 0.85 [95%CI: 0.73-0.99] per 10 years higher age), have higher baseline HbA1c (OR not reported), but also having gained weight from baseline (OR: 1.02 [1.002, 1.037]; i.e. a 2% increased risk of progression to medications with every 1lb increase in weight). It should be noted however, that no lifestyle measures (diet or physical activity), nor duration of diabetes, were accounted for within the latter analysis. Importantly, 'clinical inertia' (lack of medication intensification when clinically indicated [102, 103]) was observed for older versus younger participants, suggesting that younger participants were perhaps treated more aggressively. This 'time to medication' approach is notably limited due to the potential of clinical inertia to affect observed incidence of progression (see section 2.4.2). Additionally, the time-to-medication approach completely disregards those who experience partial progression towards failure [104]. A continuous measure for disease progression such as an assessment of beta-cell function or insulin sensitivity (section 2.4.1.2) or a rate of HbA1c

deterioration over time (section 2.4.1.3) avoids this potential misclassification of progression and accompanying information loss.

2.4.1.2 Assessing beta-cell function and insulin sensitivity

It is estimated that by the time T2DM is diagnosed, approximately 80% beta-cell function has been lost [105]. There are several methods for estimating beta-cell function and/or insulin resistance/sensitivity, each with their own advantages and disadvantages. Most are methods primarily used for research purposes rather than in routine care, and deriving parameters of interest can require highly complex modelling [106]. Comparisons between methods can also be difficult to make due to inherent test differences that stimulate different physiological pathways to greater or lesser degrees.

However, one of the simplest such measures is the Homeostasis Model Assessment 2 (HOMA2) [107]. HOMA2 indirectly assesses beta-cell function (HOMA2-%B) and insulin sensitivity (HOMA2-IS; the reciprocal of the HOMA2 of insulin resistance (HOMA2-IR)) by calculating the ratio between basal fasting glucose and insulin levels using simple equations [108, 109]. HOMA2-%B is calibrated at 100% for a normal-weight, healthy person under 35 years of age but needs to be assessed alongside values of HOMA2-IR (normal=1.0) for an appropriate interpretation. However, HOMA2-%B measures relative insulin secretion but not necessarily beta-cell health. Any use of insulin secretagogues (such as sulphonylurea medications – see section 2.3.1) can present as apparent improvements in HOMA2-%B due to their promoting of insulin-secretion as a mechanism of action. The same applies for people injecting exogenous insulin. The HOMA2 equations also become invalid upon sufficient beta-cell deterioration (fasting insulin <5 μUnits/ml) [110, 111]. As accuracy of the HOMA2 measure is therefore lost under such conditions, it was not considered a reliable index for assessing progression of T2DM. HbA1c concentrations, appropriately adjusted for glucose-lowering medication use, serve as an indirect measure of underlying beta-cell function given that higher concentrations, alongside higher medication use, will be a proxy for lower beta-cell function (and vice versa).

2.4.1.3 Modelling changes in glycaemia over time

As with diagnosis (see section 2.1), disease management is predominantly assessed using longer-term glycaemic indices (i.e. HbA1c), with National Institute of Health and Care Excellence (NICE)

guidelines recommending 'stable' HbA1c levels be measured every 6 months, or every 3-6 months if unstable [4]. HbA1c has immediate utility to both clinicians and patients as a cheap and routine metric of assessing usual blood glucose levels, 'averaging' the more acute markers of blood glucose such as FPG and PPG to provide an overall estimate of glycaemia. A potential disadvantage of HbA1c for monitoring glycaemia, aside from being unsuitable in those with haemoglobin-related abnormalities or those with chronic kidney disease [112], is that vastly different blood glucose profiles can give identical HbA1c readings on the individual level; so-called 'glycaemic variability' [37]. It is thus recommended to be interpreted by clinicians alongside other glucose measures such as FPG to appropriately assess day-to-day level glycaemic control, although this practice is uncommon prior to initiating insulin. However, no consensus currently exists on appropriate metrics for assessing glycaemic variability [113] and such data is unavailable for analysis in this thesis. For research purposes, HbA1c remains the gold-standard metric for assessing glycaemia over the long-term.

Progression of T2DM could thus be assessed in various ways. However, for the purposes of this work, T2DM progression will be assessed through modelling HbA1c trajectories adjusted for glucose-lowering medication use. This allows scope for modelling a continuous function for the varying rates of disease progression, avoids information loss as it does not require dichotomising outcomes as in previous 'time-to-medication' studies, is a routine metric of immediate clinical utility and requires data across a relatively shorter timescale compared to studies assessing time to insulin or complications.

2.4.1.3.1 Previous studies modelling medication-adjusted glycaemia over time

Several observational studies have modelled the rate at which HbA1c deteriorates or 'progresses' over time [17, 18, 104, 114–118], deriving so-called 'coefficients of failure' (CoF) for HbA1c increases in mmol/mol or % per year [104]. Glucose-lowering medication use needs to be accounted for when modelling HbA1c changes given their action on HbA1c concentrations. CoF have typically been derived in a monotherapy context [17, 104, 114–117], but more recently under conditions of changing combination (multiple medication) therapy [18, 118], most often using linear mixed effect models [17, 18, 115] or linear regressions that derive rate values individually for each participant [104, 116, 118]. Mean rates of HbA1c deterioration under monotherapy conditions range from 1.5 mmol/mol (0.14%) per year over a median four years on metformin (section 2.3.1) in n=1,454 of A

Diabetes Outcome Progression Trial (ADOPT) [17], to 3.7-5.5 mmol/mol (0.34-0.50%) per year over 10 years on sulphonylureas (section 2.3.1) in n=129 of the Oxford cohort of the UKPDS (see section 2.4.1.1) [104]. However, combination therapy is common in T2DM as the disease progresses (see section 2.3.1). Models that can incorporate effects of multiple medications simultaneously are therefore likely to reflect glycaemic trajectories that occur in the 'real-world' for most people with T2DM. Under combination therapy, mean BMI- and multiple medication-adjusted rates of glycaemic deterioration ranging from 0.69 mmol/mol (0.06%) per year over 3 years in n=625 participants of the Diabetes Research on Patient Stratification (DIRECT) 2.2 study [118], to 1.4 mmol/mol (0.12%) per year over 9 years in 5,342 participants of The Genetics of Diabetes Audit and Research in Tayside Study (GODARTS) [18] have so far been derived (see section 2.4.2 for further details). However, neither assessed for associations between modelled HbA1c deterioration and dietary patterns. Bizzotto et al [118] adjusted for multiple medication use in a conditional linear mixed model by using separate variables for metformin dose (as a percentage of maximum possible dose) and insulin use and a cumulative dose of all other glucose-lowering medications (again, as a sum of the percentage of maximum possible doses for each medication). Further information is included in section 6.1. Donnelly et al [18] on the other hand, adjusted for multiple medication use in a linear mixed model by adjusting for each individual medication and all other combinations of duel or triple therapy (76 separate combinations included as model fixed effects). This may have been feasible given the large sample size but would be unsuitable for analysing smaller samples, as in this thesis.

2.4.2 Phenotypic predictors of type 2 diabetes progression

Several phenotypic predictors of T2DM progression have been identified. A recent systematic review by Nair et al [91] of 61 studies (35 retrospective and 19 prospective cohort, 3 cross-sectional, 3 case-control studies and 1 RCT; n=50-366,955) explored predictors associating with faster T2DM progression, defined through either medication initiation/escalation, glycaemic deterioration or beta-cell deterioration. Two such studies exploring progression defined through time to insulin initiation were briefly described in section 2.4.1.1 [93, 100, 101]. The most consistent phenotypic predictors of faster progression across studies within the review by Nair et al were higher baseline HbA1c, younger age at diagnosis, high baseline adiposity (measured through either weight, BMI or waist circumference), baseline dyslipidaemia (low HDL, high LDL and triglycerides) and lower baseline beta-cell function, as measured by HOMA2-%B [91].

The only RCT included within the review by Nair et al was the Look AHEAD RCT [119]. Look AHEAD remains the largest and longest RCT involving patients with T2DM (N=5,145; duration 9.6 years) and sought to explore the effects of an intensive lifestyle intervention (consisting mainly of dietary advice and periods of low-calorie meal replacement drinks at varying frequency) on weight and CVD risk [119]. In a secondary analysis of predictors of insulin initiation during this time (n=1,087), adjusted hazard ratios (aHR) were calculated as 0.89 [95%CI: 0.81, 0.98] per 10 years of age, 1.50 [1.46, 1.55] per 10.9 mmol/mol (1.0%) higher baseline HbA1c and 1.17 [1.12, 1.23] per 5 kg/m^2 higher baseline BMI [120].

The analysis of observational data from GODARTS by Donnelly et al [18], highlighted in section 2.4.1.3.1 above, was also included within the review by Nair et al [91]. Predictors of deterioration in HbA1c trajectories over a median follow-up of 9.4 years in N=5,342 were found to be lower diagnostic age (β=1.67 [1.49, 1.85] mmol/mol (0.15 [0.14, 0.17] %) per year higher increase for diagnoses at <50 versus ≥70 years of age) and higher BMI (β=0.26 [0.06, 0.47] mmol/mol (0.02 [0.00, 0.04] %) per year higher increase for BMI ≥40 versus 25-30 kg/m^2), adjusted for multiple medications, BMI, age, sex, year diagnosed and blood-lipids [18]. In models adjusted for medications and change in BMI only, faster glycaemic deterioration was associated with lower HDL-cholesterol (β=0.60 [0.44, 0.76] mmol/mol (0.05 [0.04, 0.07] %) per year for HDL <1 versus ≥1.4 mmol/L) and higher triglycerides (β=0.36 [0.16, 0.56] mmol/mol (0.03 [0.01, 0.05] %) per year for triglycerides ≥3.5 versus <1.5 mmol/L) [18]. Similar results were obtained from a separate time-to-insulin analysis of the same cohort [94].

Described in further detail within Chapter 6, a recent analysis of the DIRECT 2.2 observational study (N=625, duration 36 months), found faster rates of glycaemic deterioration (modelled as medication- and BMI-adjusted HbA1c trajectories) associated with high visceral or liver fat (standardised coefficient (B): 0.10-0.16), deteriorating insulin sensitivity (B=-0.57), beta-cell function (B=0.28), HDL-cholesterol (B=-0.14) and triglycerides (B=0.15) and increasing endogenous insulin clearance by the liver (B=0.28) [118], in line with hypotheses of the pathophysiology of T2DM (sections 2.2 and 2.4).

Female sex has been found to associate with faster T2DM progression when measured through a time-to-medications approach in some cohort studies [91, 121–123] (adjusted hazard ratios (aHR) between 1.03 [95%CI: 1.01, 1.06] [123] to 1.2 [1.1, 1.3] [121]), but not in trial settings, where no association with sex has generally been found [101, 124], nor when including a glycaemic threshold as an additional outcome (aiming to avoid effects relating to clinical inertia; see section 2.4.1.1) [94].

A recent study exploring disparities in clinical inertia of prescribing glucose-lowering medications within UK primary care settings, found some evidence that women may be prescribed medications sooner than men (aHR: 1.05 [1.02, 1.07]) [125]. This suggests findings in studies relating female sex to faster T2DM progression could simply be an artefact of treatment inertia in men. Additionally, sex has shown no association with T2DM progression when assessed through modelled rates of glycaemic deterioration [18, 118]. Somewhat contrary to evidence indicating clinical inertia in prescribing glucose-lowering medications is greater for men with T2DM, the opposite appears to be true for medications for treating dyslipidaemia and hypertension [126, 127]. T2DM at least doubles a person's risk of developing cardiovascular disease (CVD) [128], but this risk is not shared equally between men and women. After adjusting for risk factors such as age, BMI, blood pressure, cholesterol and smoking status, the risk of coronary heart disease (CHD) and CHD mortality are 40-50% higher in women with diabetes compared to men with diabetes, and the risk of stroke is 27% higher [129–131]. Potential sex-disparities in physiology, disease treatment and efficacy of medications may help explain some of these differences [126, 127], but lifestyle differences between men and women may also play a role [33, 34] (see Chapter 4). Many of the factors associated with faster T2DM progression such as adiposity and dyslipidaemia are modifiable by diet. Ensuring healthful dietary changes are achieved in both sexes could therefore be important for minimising health inequalities between men and women.

The effects of dietary intakes on the rate at which T2DM progresses remains relatively unexplored (see section 2.7). However, to better understand the quality of evidence relating diet to glycaemia, it is necessary to first examine dietary assessment methods and how dietary patterns can be derived.

2.5 Methods of assessing dietary intake

Dietary intakes can be measured in a variety of ways. Until reliable biomarkers are identified for objective assessment of most nutrient and food intakes [132], self-reported dietary measures remain the main source of dietary data for epidemiological research. For assessing diet-health associations, a dietary measure needs to reflect usual dietary intakes over a period of time similar to that required for observing changes in a specified health marker. For example, dietary measures that can reflect usual intakes over an approximate three month period would allow for the exploration of associations between diet and HbA1c concentrations. However, no self-reported dietary measure is

perfect and all are subject to varying degrees of random and systematic measurement error [133]. This will naturally have bearing on all results presented in this thesis.

Food-frequency questionnaires (FFQs) tend to be the most commonly used method of dietary assessment within epidemiological studies. They are simple, cost-effective and aim to assess long-term dietary intakes (from 7-days to 12-months) in a relatively speedy manner [134]. FFQs take the form of checklists of varying complexity and detail and can be tailored to specific populations, assessing consumption frequencies of perhaps 100-150 foods over a preceding time-period [135]. However, FFQs rely heavily on participant memory to record foods and their average portion sizes to accurately reflect usual intakes. Food diaries on the other hand, assess dietary intakes over a specific number of days (typically 1-7), with foods and their portion sizes recorded by participants at the point of consumption. This reduces potential recall bias compared with FFQs but there is potentially greater risk of participant's altering their intakes to simplify recording or through self-reflection/reactivity [134]. This method of dietary assessment has historically been used less often within epidemiological studies, partly due to the increased participant burden, but also the logistics of collection and subsequent cost of coding data into an appropriate form for analysis [136].

Evidence indicates that multiple-day food diaries (as well as 24-hour recalls; a shorter-term dietary intake measure involving a structured interview, usually administered by a health professional) offer less biased estimates of true dietary intakes than FFQs [137, 138]. Through validation against recovery biomarkers for energy, protein, potassium and sodium, energy intake has been found to be under-reported by 18-21% in 4-day food diaries compared with 29-34% in FFQs [139]. Similarly, Prentice et al [140] found 4-day food diaries under-reported true energy intake by 20% (95%CI: 18%, 22%) whilst FFQs under-reported by 28% (95%CI: 24%, 31%). Intermediate between these two instruments were 24-hour recalls which under-reported true energy intake by 23% (95%CI: 21%, 25%) [140]. Although random error can be higher in shorter-term measures such as 24-hr recalls and multiple-day food diaries due to day-to-day within-person variation, systematic measurement error thus appears to affect multiple-day food diaries to a lesser degree compared to FFQs, followed by single 24-hr records [137, 138]. Within-person random errors inherent to shorter-term measures are also minimised if measures are repeated over time [136, 141], as they indeed are within the datasets to be analysed. Minimising dietary measurement error is naturally key for observing true diet-disease relationships. Consideration of such issues will need to be considered when analysing dietary data within this thesis (see section 6.2.2.1 for example).

2.5.1 Dietary misreporting

As discussed in the previous section, with all self-reported dietary measures there will be a risk of multiple biases affecting recorded dietary data and its subsequent interpretation. In a systematic review that investigated misreporting in 24-hour recalls and multiple-day food diaries, Poslusna et al [142] found variables most frequently associating with greater misreporting of energy intake included higher BMI, female gender, smoking and lower socioeconomic status, with under-reporting occurring in approximately 30% of people. Prevalence of dietary misreporting within an analysis of the National Diet and Nutrition Survey (NDNS) for the year 2000 was estimated to be as high as 88%, again associating under-reporting with overweight and obese individuals [143]. Systematic measurement error due to dietary misreporting thus needs to be considered during any analysis of data that incorporates self-reported dietary measures (see section 3.3.5 for example).

2.6 Dietary pattern analysis

Dietary intakes can be analysed at multiple levels, from individual nutrients to foods to whole dietary patterns. A dietary pattern describes:

"*…the quantities, proportions, variety, or combination of different foods, drinks, and nutrients … in diets, and the frequency with which they are habitually consumed.*" [144]

Dietary pattern analysis acknowledges that people do not eat single nutrients or foods, but combinations of nutrients within many different foods. Changing food intakes to modify one nutrient invariably changes many nutrient intakes simultaneously. Background dietary intakes may thus confound observed relationships when studying the effects of single-nutrients on health. Investigating the effects of single nutrients may be appropriate in diseases of deficiency, but diseases such as T2DM have a complex aetiology with multiple nutrients/food implicated (see sections 2.7.1 and 2.7.2). A dietary pattern approach to studying T2DM is therefore likely to be more informative [145], plus food-based eating recommendations translate more easily for members of the public to follow [146]. On a practical level, separating individual nutrient effects can be difficult if collinearity exists between two or more nutrients simultaneously [147]. However, such collinearity can be accounted for within a dietary pattern as patterns are inherently characterised by usual consumption of combinations of foods, in turn reflecting real-world eating behaviours [148]. Dietary patterns typically require grouping foods together by nutrient profiles and/or common culinary

usage in order to simplify interpretations (see sections 2.6.1.2 and 2.6.1.3). This reduces the number of variable dimensions and in turn the number of subsequent hypothesis tests, lowering the risk of finding chance associations between diet and health where there are in fact none. On the other hand, studying multiple nutrients simultaneously within a dietary pattern may provide a more detectable effect on outcomes compared with investigating the effect of one nutrient alone [148].

In line with the above, current management guidelines encourage people with T2DM to follow suitable dietary patterns rather than specifying single nutrient intakes [20, 21].

2.6.1 Methods for defining dietary patterns

2.6.1.1 '*A priori*' methods

A priori dietary pattern methods, such as dietary indices, are often used to measure levels of adherence to predefined dietary patterns or guidelines. Dietary pattern indices are developed using existing knowledge on relationships between diet and health/disease. Maximum and minimum scores aim to reflect the conceptualised maximum and minimum level of adherence to that particular dietary pattern [147, 149]. Composition of such indices involves a number of subjective choices relating to those variables or items deemed relevant for inclusion, including cut-off values and the scoring system itself [150, 151]. Examples of a priori dietary pattern indices include the Healthy Eating Index (HEI), Alternate Healthy Eating Index (AHEI) plus multiple indices for assessing adherence to the Mediterranean diet (see section 2.7.3.2).

Although scientific evidence should be employed in dietary index development, they are limited by the current state of this knowledge and the subjectivity with which evidence is deemed most important. Inter-correlations between different dietary components may also not be adequately addressed when summated scores are calculated from non-adjusted effects of single items/components [29, 147]. Mid-range scores fail to indicate which dietary components are being followed and which are not, meaning that those most informative are high-end and low-end scores [152]. Capturing variation present in dietary intakes by a given dietary pattern index will thus not always be adequate if that pattern is not being followed by that population. *A priori* methods however remain a simple method for assessing diet quality as cheaply and quickly as possible at population level. Evidence for relationships between glycaemia and a priori dietary pattern scores are discussed in section 2.7.3.2.

2.6.1.2 'A posteriori' methods

Data-driven (*a posteriori)* methods for deriving dietary patterns are exploratory in nature, using a variety of multivariate statistical techniques to identify commonalities or intercorrelations within empirical dietary data [147]. Methods most commonly seen within the literature include principal component analysis (PCA), factor analysis and cluster analysis. PCA and factor analysis are both dimension-reduction techniques, transforming original sets of correlated variables into smaller sets of uncorrelated variables called 'principal components'/'factors' [149]. Similarly, cluster analysis is a dimension-reduction technique that instead transforms original data into clusters/sub-groups based on correlations between food intakes amongst study participants [153]. *A posteriori* dietary patterns are based on empirical data only and do not necessarily represent optimal patterns relating to good health [148]. Unlike *a priori* methods, *a posteriori* methods ignore prior knowledge completely, maximising variation in any food intakes that exist within a population.

2.6.1.2.1 Principal component analysis (PCA) and Factor analysis

PCA is a form of factor analysis that involves an orthogonal linear-transformation from the data coordinate system to a new coordinate system (based on the correlation or covariance matrix of predictor variables), projecting the original data into its 'principal components'. The first components accounts for as much total variation of the predictor variables as possible [147, 149, 154]. The second component then accounts for as much of the remaining variation as possible, and so on. Higher-order components tend to be ignored as contributions to the data variance become insignificant [149, 154].

In the case of dietary patterns, each principal component is a linear combination of weighted food group intakes (relative to their correlation with the overall intercorrelation of food groups), scored through summing the products of the reported intake of each food group with its correlation weighting [152, 154]. Care must be taken should only the highest scoring principal component be taken to be reflective of an individual or group's actual dietary pattern when another high scoring principal component/dietary pattern is also evident [154]. This is true for all data-driven dietary pattern methods where multiple factors are extracted.

'Common' factor analysis is like PCA but differs fundamentally in its approach to dimension reduction. It assumes the presence of a latent variable/factor which has a weighted influence on a set of observed variables (food groups in the case of dietary pattern analysis) and can thus be conceptually considered to be *causing* responses in these observed variables [155]. Unlike in PCA, 'error' terms are also created in factor analysis that are associated with the observed variables' remaining variance left unexplained by that factor (often referred to as the 'unique variance'). These factors are however still essentially modelled as weighted linear-combinations of observed variables (food groups) as in PCA, albeit plus error terms, and the two methods produce equal results when the factor analysis error-terms are assumed to have equal variance [156].

2.6.1.2.2 Cluster analysis

Whereas PCA and factor analysis produce dietary patterns through grouping intercorrelated food groups together, cluster analysis works through grouping study participants together [147], building 'clusters' of individuals with similar dietary patterns based on mean food group intakes. Choosing the appropriate number of clusters can be a subjective decision made by the researcher [153], although additional criteria does exist [152]. The main difference in output between these methods is that cluster analysis produces a single dietary pattern per grouping of study participants, whereas PCA and factor analysis produce a variety of continuous pattern scores per study participant, albeit with varying degrees of captured variance in food group intakes.

Although useful for identifying dietary pattern sub-groups within a population, in cluster analysis, individuals are categorised into whichever cluster their diet is closest to, reducing analysis power to assess associations with health from multiple dietary pattern categories [154]. Importantly, categorising an individual into a cluster that their own dietary intake is closest to will inherently lead to some degree of information loss at the individual-level.

2.6.1.3 Hybrid a priori/a posteriori methods

The dietary patterns derived through PCA, factor or cluster analysis can demonstrate similarities with one another but also differences [157, 158] and theoretically could provide complementary insights to one another. Inherently however, they do not consider disease-relevant endpoints in their pattern construction. Such patterns may thus be sub-optimal for explaining diet-disease

associations as they maximise variation in food intakes only and not in any nutrients/biomarkers that might link diet with health status. Potentially causal relationships between diet and disease are therefore left uninformed. 'Hybrid' methods that instead combine advantages of both *a priori* and *a posteriori* methods, such as reduced-rank regression, aim to alleviate this problem.

2.6.1.3.1 Reduced-rank regression

Reduced-rank regression (RRR) determines weighted linear functions of predictor variables (food groups in this case) by instead maximising the explained variation in *response* variables (disease-mediating nutrients or biomarkers) [29]. This differs from PCA, for example, which maximises the explained variation in *predictor* variables/food group intakes (section 2.6.1.2.1). Similar to other factor analyses, the first derived factor from RRR explains a higher amount of variation in response variables than any subsequent derived factor [29]. Derived factors (dietary patterns) are again a linear combination of standardised food group intakes, each multiplied by their respective factor loading [159]. However, whereas PCA/factor analysis aims to maximise the explained variation in multiple *food group* intakes simultaneously, RRR aims to maximise the explained variation in multiple disease-relevant *nutrient intakes or biomarker*s simultaneously. The dietary pattern produced is based on observed real-world co-variation in both food and nutrient intakes (or biomarker values). Any subsequent associations found between dietary patterns derived via RRR and health outcomes can in turn be interpreted through either the particular combination of foods, the combined differences in the specified intermediate nutrient intakes/biomarkers, or both. This offers obvious advantages over other pattern-derivation methods whereby mechanisms of action are left uninformed. To justify this approach however, prior knowledge or theory should be used to inform the choice of intermediate response variables relating diet with disease [29] (see section 2.7.1). In this way, RRR can be considered a 'hybrid' method invoking both *a-priori* knowledge and *a-posteriori* data-driven approaches. The maximum number of extracted factors equals the number of response variables specified and, as in PCA, extracted factors are orthogonal and therefore uncorrelated with one another [29].

By its very nature, RRR dietary patterns explain greater variation in response variables compared to other pattern derivation methods. For example, in a study by Melaku et al [160] that evaluated differences between data-driven dietary patterns, total variation explained in protein, calcium, potassium and vitamin D intakes by the first extracted dietary pattern was 28.3% using RRR versus 24.9% using PCA [160]. Although RRR in turn explains less variation in food intakes (3.4% using RRR

versus 10.3% using PCA in the study by Melaku et al [160]), it limits the ways in which food intakes vary to only those that overlap with potential disease mechanisms. RRR can remove the extraneous variation or 'noise' from differences in food intakes that do not contribute to the disease process. In line with this, stronger associations are typically seen with health outcomes using RRR compared to other methods [160–164].

As mentioned, chosen response variables in RRR dietary pattern analysis should be considered potential mediators between diet and disease and can be specified to be either nutrient intakes or biomarkers. However, greater variation in response variables is typically captured by RRR-factors where nutrients have been chosen as RRR responses, rather than biomarkers. For example, within the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study, Schulz et al [165] extracted a dietary pattern of 39 food groups that explained 42.8% total variation in saturated, monounsaturated, and polyunsaturated fat intakes, whereas a dietary pattern of 48 food groups extracted in the same cohort with HbA1c, HDL-cholesterol, C-reactive protein and adiponectin as response biomarkers explained only 14.5% total response variation [166]. Dietary patterns constructed using nutrient RRR responses may thus be more informative as greater variation can be explained in proposed diet/disease relevant pathways. Biomarkers also tend to be subject to multiple influences beyond diet, whereas nutrient intakes will be more proximal to an individual's dietary pattern.

A common misunderstanding of RRR is that subsequent associations between diet and disease are 'built-in' during the dietary pattern's construction because the disease-related intermediate response variables are chosen by the researcher. However, any such 'self-fulfilling' associations are minimised when using nutrients as RRR responses as these are more proximal to diet, rather than biomarkers which may indeed be acting as proxies for the disease itself. Nutrients as diet-disease intermediates should only produce self-fulfilling associations in as far as the chosen nutrients are true mediators between diet and disease and only to the extent that diet co-varies, via nutrient intakes, with disease outcomes within collected data.

Comparing data-driven dietary patterns derived through either *a posteriori* or hybrid methods between studies can be difficult [167]. Given that the general purpose of deriving such patterns is to establish relationships with health, data-driven dietary patterns would ideally be found to be stable (i.e. the same relative order and loading of constituent food groups) and therefore reproduceable at group-level in external samples to claim validity for the greater population or subpopulation. In a systematic review of dietary patterns derived through different methods and their subsequent

associations with T2DM incidence, Jannasch et al [167] concluded that that many data-driven dietary patterns remain population-specific and can therefore only serve as single observations (see section 2.7.3.3 for further information). Extracted dietary patterns can also be named similarly between studies, such as a 'Western' or a 'Prudent' dietary pattern, yet differ in the food groups which load prominently onto the pattern scores, thereby representing different constructs [167]. Furthermore, the condensing of foods into food groups for dietary pattern analysis is largely subjective and studies can report dietary patterns with varying numbers of food groups with differing component foods; again, making formal comparisons of data-driven dietary patterns between studies difficult [167]. Under such circumstances, comparison of data-driven dietary patterns from different cohorts are generally limited to narratively assessing similarities between the different component food groups.

In summary, dietary pattern analysis acknowledges that in the real-world, people do not eat single nutrients or foods but combinations of multiple nutrients and foods. Data-driven dietary pattern methods capture these 'real-world' intakes of multiple foods simultaneously and can subsequently explore associations between holistic diet and health outcomes. However, mechanisms of action of such dietary patterns on health outcomes are left uninformed. The hybrid method of RRR helps bridge this gap, deriving patterns from empirical dietary data whereby theorised nutrient-based mechanistic pathways are inherently built in, elucidating the potential mechanisms of action between dietary pattern and disease. Given its advantages over other data-driven methods, RRR is the chosen method for dietary pattern derivation throughout this thesis.

2.7 What is known about diet and glycaemia in type 2 diabetes?

Diet advice is the cornerstone of treatment for T2DM [21]. The following sections explore the evidence base relating diet (either nutrients, foods or dietary patterns) and its effects on glycaemia in T2DM. Current literature has explored effects of diet on shorter-term changes in glycaemic control only, rather than effects on longer-term glycaemic deterioration relating to a decline in disease state. Relatively few studies, especially RCTs, are of duration longer than 12 months. Studies also typically report HbA1c differences over time in absolute terms, rather than in terms of rates of change. Although rates of HbA1c change could be inferred at group-level from average HbA1c differences observed over a particular study period, shorter follow-up periods may not be

representative of how glycaemia changes over the longer-term, especially given most trials include an intervention component. Therefore, as studies examining diet's specific effects on glycaemic deterioration are scarce, evidence will be reviewed for any effects on glycaemia attributable to particular dietary components in established T2DM. Where this is not available, studies exploring associations between diet and incidence of T2DM are highlighted.

2.7.1 Glycaemic effects of specific nutrients

Glycaemia is contributed to by both FPG and PPG. Associations have been demonstrated between PPG after breakfast and HbA1c, between FPG and HbA1c, and between the changes in FPG and PPG with those of HbA1c [168]. Nutrients observed to impact either FPG, PPG or HbA1c could therefore be considered a risk factor for impacting glycaemic control and perhaps subsequent glycaemic deterioration in T2DM.

2.7.1.1 Carbohydrates

Dietary carbohydrates are the main determinant of PPG levels [24]. However, carbohydrates are a heterogeneous class of nutrients whose metabolic effects differ with their digestion and absorption mechanics. A classification based purely on chemical structure is not suitable to predict their effects on health, thus classification based on digestion and absorption capacity within the small intestine appears most appropriate [169]. Digestible-carbohydrates can be considered those that are associated with a post-prandial rise in blood glucose levels in a dose-response manner. In general, these consist of starches (polysaccharides) and sugars (mono- and di-saccharides). Non-digestible carbohydrates (essentially, dietary fibres) are those carbohydrates that are not digested and absorbed in the small intestine, and are not associated with a post-prandial rise in blood glucose levels [169]. Changes in PPG will thus be affected by both quantity and quality of carbohydrates, with the majority of foods containing mixtures of both digestible and non-digestible carbohydrates in varying proportions [170].

2.7.1.1.1 Starches and sugars

The nature of a starch or sugar is known to influence their digestibility and hence PPG response [171, 172]. Different starch types and their ratios, as well as their cooking and processing method, have been shown to influence starch digestibility [173, 174]. However, self-reported dietary measures (section 2.5) are inevitably unable to capture this level of detail in starch intakes. Starches are thus typically grouped together, as they are in this thesis, as carbohydrates that overall lead to an increase in PPG levels.

There currently appears no strong evidence suggesting differential effects on glycaemia between different dietary sugars. A meta-analysis of 10 controlled-feeding trials of isocaloric exchange of fructose for other carbohydrates (mostly starches and/or sucrose, with background diets consisting of 50-55% carbohydrate, 20-35% fat, 15-30% protein) in 134 T2DM patients found no effects of fructose replacement on HbA1c (Mean Difference (MD) [95%CI]: -1.4 [-3.7, 1.0] mmol/mol (-0.13 [-0.34, 0.09] %)) [175]. Median trial duration was however only 8-weeks; shorter than the typical 12-week HbA1c turnover period, and results are further limited by the small sample size. Diets containing 25% of total energy from fructose-sweetened rather than glucose-sweetened beverages have been shown to increase visceral adiposity in healthy subjects who are overweight/obese [176]. Hepatic insulin resistance has also been associated with fructose intakes from sugar-sweetened beverages (SSB), potentially contributing to the liver-pancreas dysfunction characteristic of T2DM (section 2.2). However, a recent meta-analysis of 108 controlled energy-substitution studies appeared to show small improvements in HbA1c (MD: -2.4 [-3.8, -0.9] mmol/mol (-0.22 [-0.35, -0.08] %)) when exchanging non-fructose- with fructose-containing foods, potentially weighted towards studies where fruit was the substitution [177]. Median duration of these substitution studies was only 4.5 weeks however, and only 37/108 studies were in individuals with T2DM, calling into question the generalisability of results.

2.7.1.1.2 Fibre

PPG response has been shown to be modulated by the amount and type of dietary fibre. Most fibre-rich foods contain a mixture of both soluble and insoluble fibres in varying ratios [169]. Viscous soluble fibre has been shown to slow gastric emptying and delay glucose absorption in the small intestine, improving PPG control [25]. Dietary fibres accessible by gut microbiota produce short-chain fatty acids (SCFA) that stimulate adipocytes to secrete gastric inhibitory polypeptide, peptide YY and glucagon-like peptide-1 (GLP-1), which leads to reduced fat accumulation [178, 179]. An

umbrella review of RCT meta-analyses assessing HbA1c in relation to fibre intake in T2DM (35 RCT's, N=1734) reported mean HbA1c reductions in 4 out of 5 meta-analyses, ranging 2-6 mmol/mol (0.21-0.52%) [180]. Mean duration of trials ranged from only 4.5-11 weeks, suggesting longer-term effects on HbA1c may be higher. However, all included trials used supplemental soluble fibre. A more recent meta-analysis of 16 RCTs (N=747 with T2DM) included 4 studies where fibre was increased via foods rather than supplementation (thus a combination of soluble and insoluble fibre) and found similar results [181].

There appears little evidence specifically associating insoluble fibre with T2DM management, although it is consistently linked with reduced T2DM incidence in prospective studies [182–184]. Evidence also indicates it is linked with improved whole-body insulin sensitivity in healthy subjects [185, 186].

2.7.1.1.3 Understanding the role of carbohydrates in glycaemia

There have been many systematic reviews and meta-analyses of RCTs exploring the effects of carbohydrate-restricted diets on glycaemia in T2DM [187, 188, 197, 198, 189–196]. Many of these reviews/meta-analyses contain the same primary RCTs and are therefore not strictly independent, but nevertheless, evidence indicates low-carbohydrate diets (defined in Table 2.1) associate with reductions in HbA1c over the shorter-term only (duration 6-12 months). The most recent meta-analysis of RCTs by Jayedi et al [198], compared effects of low-carbohydrate diets with low-fat diets (80% trials) or 'healthy diet' advice (20% trials) and determined a dose-response on HbA1c of -2.2 [95%CI: -3.0, -1.4] mmol/mol (-0.20 [-0.27, -0.13] %) at 6 months (29 trials; n=2461) and -1.2 [-2.0, -0.5] mmol/mol (-0.11 [-0.18, -0.05] %) at 12 months (13 trials; n=1222), for each 10% reduction in total energy from carbohydrate (across an intake range of 55-65% to 10% total energy).

Table 2.1: Currently accepted definitions of carbohydrate intake levels [199]

Carbohydrate intake level	**Grams per day (based on 2000kcal diet)**	**% total energy intake**
Very-low	20–50	6–10
Low	<130	<26
Moderate	130–225	26–45
High	>225	>45

However, there are a number of major caveats associated with interpreting such results that apply to all meta-analyses in this area (many of which also apply to the primary RCTs included therein). Firstly, there is considerable heterogeneity between trials, meaning drawing firm conclusions is difficult. The duration of trials within present meta-analyses [187, 188, 197, 198, 189–196] range from 4-weeks to 4-years (n=645 to 4937), with 'low-carbohydrate' intakes stated as ranging from 20g/day up to 45% total energy. The median trial duration in the recent meta-analysis by Jayedi et al [198] was only 5.5 months, meaning long-term inference on glycaemia outcomes was largely uninformed. Importantly, meta-results from combined trials are invariably confounded by differences in the amount of carbohydrates within intervention diets (many being mislabelled as 'low-carbohydrate' yet contained much higher amounts, for example 43-44% total energy from carbohydrates in a trial by Esposito et al [97]), the amount of accompanying weight loss, varying assessment of and degree of diet adherence, the background diet (amount and quality of other nutrients and foods being consumed, including the overall dietary pattern, external to the intervention target), and reporting on medication use.

As mentioned in section 2.3.2.1, weight loss is itself associated with improvements in glycaemia. It can be extremely challenging therefore to differentiate the independent effects of macronutrients on glycaemia from that induced by weight loss. A low-carbohydrate diet itself can be a suitable option for people with T2DM to induce weight loss [21], potentially aided by spontaneous reductions in *ad libitum* energy intake observed when adopting such diets (in particular with very-low carbohydrate/ketogenic diets) [200–202]. However, current evidence suggests that when energy intakes are equivalent, low-carbohydrate diets do not produce greater weight loss than any other diet [202–204]. It is thus unclear whether following an 'extreme' form of diet is necessary if the chief mechanism of action on glycaemia is via accompanying weight loss, which could be similarly achieved through a variety of other diets.

A further issue affecting interpretation of the effects of low-carbohydrate diets is that adherence to low-carbohydrate diets can often be poor [205], and as with many dietary interventions, can decline over time [206]. A notable example is an RCT by Iqbal et al [207], which provided monthly dietitian-led group counselling in 125 people with T2DM and obesity to follow either a low-fat (<30% total energy) or 'low'-carbohydrate (<30g/day) diet. After 2 years, carbohydrate intakes differed by only 8g between groups [208] with approximately equal energy intake and ~47% dietary energy coming from carbohydrates [207]. Trials, and thus meta-analyses grouping these trials, evaluating effects of

prescribed rather than actual dietary intakes offer little information on diet's true effects in T2DM. Jayedi et al [198] noted how 10 out of 11 trials studying effects of very-low carbohydrate diets failed to meet the threshold for this low level of carbohydrate intake and thus could not be analysed as such. Although not confirmed, poor adherence to such extreme diets may explain the diminished benefits seen for lower-carbohydrate diets on glycaemia over periods of 12 months or longer [205]. Poor adherence to any diet is a likely indication of what might or might not be achievable within usual diabetes care. Trials randomising participants to diets that the participant would not ordinarily choose and/or is unable to follow are therefore likely to continue to produce poor quality evidence unless dietary adherence can be accounted for appropriately[209].

However, a key limitation in much of the diet-related T2DM literature, and of key importance for this thesis, is that background diets (i.e. the differences in dietary intakes outside of the specific target of a trial intervention) are rarely kept the same or reported in sufficient detail. Analysing the effects of low-carbohydrate versus other dietary interventions are typically misleading, as although diets may be similar in specific nutrient intakes, they can be widely dissimilar in all other aspects of the diet [210]. For carbohydrates specifically, total intakes between two diets may be similar but the quality of carbohydrate may differ. For instance, although not always reflecting how 'healthful' a food is, the glycaemic index (GI) of a carbohydrate-containing food is a measure of the relative rate at which that food increases blood glucose levels compared with a test food (often pure glucose). The glycaemic load (GL) of a food then combines the GI value with the typical portion size consumed to classify the real-world impact on blood glucose that food is likely to have. Despite similar total carbohydrate levels, lower GI/GL diets have been associated with small but overall greater reductions in HbA1c compared with higher GI/GL diets (MD: -3.4 [-4.6, -2.1] mmol/mol (-0.31 [-0.42, -0.19] %); meta-analysis of 29 RCTs in people with type 1 or 2 diabetes [211]). Additionally, comparing effects of a low-carbohydrate with a low-fat diet, for example, on health outcomes will not produce results reflective of this 'single' difference. Low-carbohydrate interventions have also typically been high-protein interventions (>25% total energy) [198]; the independent role of carbohydrates or proteins or fats on glycaemia therefore remains largely inconclusive. The sections that follow discuss the evidence base for the effects on glycaemia of different types of fat, protein and specific foods, all of which may vary and potentially impact glycaemia despite an individual following an otherwise identically labelled diet.

Low-carbohydrate diets do however appear to associate with reduced requirement for glucose-lowering medications [191, 192, 197, 212–214]. Individual trials have typically failed to adequately report medication usage or changes under different dietary regimes in a uniform way and thus

meta-analyses have so far been unable to pool this data [210]. Therefore, Wheatley et al [210] performed a narrative review of trials included in many of the aforementioned meta-analyses [188, 190, 216, 217, 191, 192, 195, 197, 212–215] where trial duration exceeded 3 months, N>50 and low-carbohydrate diets were classified appropriately (<130g/day) based on participant self-reporting. Only six out of the 71 trials met this criteria [201, 218–222], with low-carbohydrate diets improving HbA1c in only one [219]; a comparison against a low-GI diet containing a self-reported 44% energy from carbohydrates. However, all trials that reported medication use as an outcome demonstrated greater reductions in glucose-lowering medications in participants randomised to the low-carbohydrate diet [201, 219–222]. Reduced medication requirements during carbohydrate restriction suggest that such diets can reduce HbA1c concentrations to a greater degree than implicated by only comparing intervention/control group HbA1c means. This finding is understandable given the chief contributor to PPG levels has been removed from the diet, thus rendering glucose-lowering medications largely redundant. However, a withdrawal of medications alongside apparent improvements in glycaemia isn't necessarily reflective of an improved disease state, as subsequent re-introduction of carbohydrate would be expected to return blood glucose back above normal levels. This may be irrelevant to people able to adhere to such diets but could lead to significant hyperglycaemia and/or glycaemic variability [37] if adherence is poor and medications have been withdrawn. It is also unknown at this stage whether reduced medication use whilst following low-carbohydrate diets is durable over the long-term without additional weight loss, and likewise, whether diets that vary in carbohydrate content associate with rates of glycaemic deterioration.

2.7.1.2 Fatty acids

As with other macronutrients, there is no specific recommendation for optimal dietary fat intakes in T2DM. This is primarily due to mixed evidence in relation to potential contributions of fat intakes on dyslipidaemia and CVD risk [20, 21]. However, fatty acids have been shown to potentially affect glycaemia. *In vitro* studies indicate that fatty acids induce a pleiotropic effect on beta-cell function; changing cell signalling, insulin secretion, mitochondrial metabolism, and composition of beta-cell membranes [52]. The effects of specific fatty acids on insulin secretion and rates of beta-cell loss appear to be directly related to the degree of saturation and chain length, with chronic exposure of beta-cells to unsaturated fats increasing glucose-stimulated insulin-secretion and beta-cell survival [26, 223]. Chronic exposure to palmitate on the other hand (a common dietary saturated fat (SFA) but also the main product of *de novo* lipogenesis; a process heightened in T2DM and contributing to

ongoing hepatic-pancreatic dysfunction [224]; see section 2.2), has been shown to decrease beta-cell secretory function and insulin gene expression [52, 225, 226].

In vitro evidence suggests that SFA can increase skeletal-muscle insulin resistance through activating pro-inflammatory cascades and promoting intracellular ceramide synthesis [227, 228]. *In-vitro* experiments indicate that oleate (a monounsaturated fat) can divert palmitate (a saturated fat) away from ceramide synthesis, preventing cellular ceramide accumulation and therefore insulin resistance [227, 229]. There may also be additional effects on insulin sensitivity due to MUFA through conservation of insulin signalling pathways [230, 231]. Possible glycaemic control mechanisms related to polyunsaturated fats (PUFA) include their anti-inflammatory potential for reducing insulin resistance, suppressing *de novo* lipogenesis [232], increased GLUT4 translocation (moving of glucose into cells), plus both direct and indirect effects on insulin secretion [233, 234].

In vitro models do not necessarily mimic the physiological environment *in vivo* [232]. However, a systematic review and meta-analysis by Imamura et al [228], compared SFAs, MUFAs, PUFAs, and carbohydrates for their effects on glucose-insulin homeostasis in adults within relatively short (median 28-day) randomised controlled feeding trials. Dose-response effects of isocaloric nutrient replacement in a T2DM sub-group analysis (18/23 trials) demonstrated replacement of carbohydrates with PUFA or MUFA produced favourable effects on HbA1c. A 5% energy replacement of carbohydrates (mostly refined starch and sugars) with PUFA or MUFA was found to improve HbA1c by -2.0 [95%CI: -3.6, -0.3] mmol/mol (-0.18 [-0.33, -0.03] %) and-1.7 [-2.7, -0.7] mmol/mol (-0.16 [-0.25, -0.06] %) respectively. Low trial duration is a factor here given the typical turnover for HbA1c is ~3 months and final changes could therefore be greater than reported. However, a separate meta-analysis by Schwingshackl et al [235] of 5 longer-term RCTs (duration 1-4 years, N=667) comparing high- (>12%) versus low-MUFA (≤12%) diets in patients with T2DM demonstrated that high-MUFA diets were associated with decreases in HbA1c compared to low-MUFA diets (-2.3 [-4.4, -0.2] mmol/mol (–0.21 [–0.40, –0.02] %)).

A more recent meta-analysis of 24 RCTs (N=1460) by Qian et al [236], claimed iso-caloric substitution of carbohydrate with MUFA in people with T2DM did not reduce HbA1c over a mean follow-up of 19-weeks (-0.9 [-1.6, 0.0] mmol/mol-0.08 [-0.15, 0.00] %) but did reduce FPG (-0.57 [-0.76, -0.39] mmol/L). Mean diet composition in the high-carbohydrate group was 54% carbohydrate, 17% protein, 28% fat (11% MUFA) and in the high-MUFA group, 39% carbohydrate, 17% protein, 43% fat (25% MUFA). Stratified post-hoc analysis found modestly greater changes in HbA1c in trials that were of longer duration (>6 weeks), consistent with the short duration of most studies included

(18/24 trials were ≤3 month duration) and the longer-term nature of the HbA1c measure. However, interpreting such evidence in terms of mean dietary compositions after grouping trial interventions is misleading. There is inevitably variability in dietary composition within intervention and comparator groups (in the high-MUFA grouping for instance, dietary intakes ranged between 10-49% MUFA and 10-46% carbohydrates). As discussed in section 2.7.1.1.3, it is difficult to reach concrete conclusions on which aspects of diet are producing observed effects when background diets can vary in multiple ways.

Small improvements in glycaemic markers may be expected when replacing dietary carbohydrates with other macronutrients, given the known effects of digestible carbohydrates on blood glucose (section 2.7.1.1.1). However, in the meta-analysis by Imamura et al [228], no evidence was found for glycaemic changes when replacing carbohydrate intakes with isocaloric amounts of SFA like there was with MUFA and PUFA replacement. The quality of fat for replacing carbohydrate therefore appears to be important. Unless appropriately planned, diets low in carbohydrates may lead to a concomitant increase in total dietary fat, and in turn SFA, potentially negatively impacting insulin sensitivity whilst increasing CVD risk [237, 238].

2.7.1.3 Proteins

Certain amino acids have been shown to directly and/or indirectly stimulate insulin secretion [27, 239], potentially helping reduce PPG excursions when consumed in combination with carbohydrates [240]. Several small (N=8-12), short-term (5-10 weeks) controlled trials with full food provision aimed to maintain body weight (though small weight losses ~1.8kg did occur) but increase the proportion of dietary protein (from 15% to 30% total energy) to observe effects on glycaemia in T2DM [241, 242]. Results indicated improvements in a range of glycaemic markers such as HbA1c (a reduction of 27 mmol/mol (2.5%) after 10 weeks from an initial (high) mean HbA1c of 86 mmol/mol (10.0%) [242]). Another small (N=28), short-term randomised crossover trial (6 weeks followed by 6 weeks, without washout period) aiming to maintain weight by Skytte et al [243], found a diet with 30% versus 17% energy coming from protein reduced mean HbA1c by 6.2 mmol/mol (0.6%) versus 0.75 mmol/mol (0.1%) respectively. Weight loss was slightly greater in the higher-protein group (-1.4kg vs -0.8kg) but was not found to be significant. However, carbohydrates in these studies were also restricted to a greater degree in the higher protein diets, so it is unclear what role protein in particular played in contributing to these results.

Appropriately designed trials of longer duration in larger samples are necessary. High-protein diets over the long-term potentially increase levels of insulin resistance [244] and have been associated with an increased risk of T2DM [245]. A recent meta-analysis of 13 RCTs (N=1,138) of duration ranging 3-24 months found no differences between high-protein (defined as >25% total energy) or lower-protein diets on HbA1c in T2DM, but as with many meta-analyses in this area, weight loss varied between included studies, glucose-lowering medication use was not considered, and prescribed rather than recorded intakes were used to define diets. For example, one of the included studies (duration 12-months; N=419) found no difference in HbA1c between high and low-protein groups but both groups' mean protein intakes were in fact recorded to be the same at each timepoint (19-22% total energy) [246]. Therefore, although protein is known to increase feelings of satiety which may aid with weight loss [247], evidence for its role in glycaemic management outside of this remains unclear.

2.7.2 Glycaemic effects of specific foods or food groups

Relatively little high-quality evidence exists for the isolated impact of specific foods on glycaemia in T2DM compared to that attributed to individual nutrient intakes or overall dietary patterns. As it is difficult to assess the effects of only single nutrients, it is also difficult to isolate the effects of any one food on glycaemia when free-living individuals typically consume diets containing a mixture of foods and quality of nutrient intakes. The following sections however, aim to describe present evidence exploring potential effects on glycaemia of specific foods or food groups on glycaemia in T2DM, serving as a bridge between effects of single nutrients (section 2.7.1) and effects of combined nutrient and food intakes in the form of dietary patterns (section 2.7.3).

2.7.2.1 Nuts

Current evidence for effects of nuts on glycaemia in T2DM is mixed. A recent meta-analysis of 7 RCTs (durations ranging 2-12 months; N=313 total participants) found no evidence of effects of almonds or walnuts (in addition to usual diet or through energy replacement) on HbA1c at any timepoint examined [248]. Only one included trial (duration 3 months; N=100) found evidence of a benefit to HbA1c with walnut oil supplementation (-0.63 mmol/mol (-0.06%)) versus no intervention (0.01 mmol/mol (0.0%)), despite bodyweight maintenance, although potential dietary changes elsewhere in the diet were not reported [249]. However, another recent meta-analysis of 6 short-term RCTs

(duration 12-16 weeks; N=174 total participants) exploring effects of almonds on glycaemia in T2DM found that almond consumption led to improvements in HbA1c (MD [95%CI]: -5.7 [-6.3, -5.0] mmol/mol (-0.52 [-0.58, -0.46] %)) [250]. The longest trial included (16 weeks) was a double-blinded, crossover RCT in 30 T2DM participants [251] which found no differences between 4-week long diets with 25% or 37% total energy from fat, with or without 10% energy from almonds or from olive/canola oil on either HbA1c, FPG or insulin levels. Again, as described in section 2.7.1.1.3, trial interventions in such meta-analyses are typically heterogenous, with some interventions adding almonds to usual diets whilst others compared effects between different types of nuts combined with a low-carbohydrate diet [252], including varying bodyweight changes.

Although nuts are a source of additional fibre and MUFA/PUFA, potentially aiding glycaemic control, there is currently insufficient quality of evidence to conclude that nut intakes independently affect glycaemia in T2DM. Various meta-analyses of chiefly observational data have also failed to associate nut consumption with incidence of T2DM [253–255].

2.7.2.2 Oils

The majority of literature investigating effects of oils on glycaemia in T2DM relates to olive oil (an oil high in MUFA and the main source of fat attributed to the Mediterranean diet pattern (see section 2.7.3.1)). A meta-analysis of 22 RCTs (durations ranging 2 weeks to 4 years; N=3698 with T2DM) found greater reductions in HbA1c (-3.8 [-5.2, -2.5] mmol/mol (−0.35 [−0.48, −0.23] %)) were associated with diets higher in olive oil rather than low-fat diets, but found no differences between diets rich in PUFA- or supplemental fish-oil [256]. This meta-analysis was predominantly weighted by a 4 year trial (N=215) by Esposito et al [97], which compared effects of an energy-restricted Mediterranean style diet containing 30-50 grams of olive oil (>30% total energy from fat) per day with a low-fat diet (<30% total energy from fat) on glycaemia (this trial is discussed further in section 2.7.3.1). The olive-oil supplemented diet in this trial coincided with an overall delayed need for initiating glucose-lowering medications, suggesting potentially delayed glycaemic deterioration. Group mean differences in HbA1c at 4 years favoured the olive oil/Mediterranean diet (-4.4 [-9.8, -1.1] mmol/mol (-0.4 [-0.9, -0.1] %)) but this did not reflect differences in medication use between groups, suggesting effects on HbA1c may have favoured the olive oil intervention to an even greater degree. However, the olive-oil/Mediterranean diet was also lower in carbohydrate intakes by 8-10% total energy compared with the low-fat diet, and cumulative weight loss was found to be greater in the olive oil/Mediterranean diet group during subsequent follow-up [98]. Background diets were

also not reported in detail meaning any specific effects attributable to olive oil consumption over other factors is unclear.

2.7.2.3 Meat, poultry and fish

No trial or observational evidence could be found linking meat, poultry or fish's specific effects on glycaemia in T2DM. However, a number of meta-analyses and umbrella meta-analyses have linked higher total, red and processed meat intakes with greater risk of T2DM [254, 255, 257, 258]. Poultry and fish intakes have not been identified to have a specific effect on risk of T2DM [255].

2.7.2.4 Dairy

There is very limited literature exploring the specific effects of dairy foods (such as milk, yogurt, cheese or butter) on long-term glycaemia in T2DM. Evidence currently suggests no differences in glycaemia in T2DM from consuming less than or more than 3 servings of dairy milk of varying fat content per day (RCT of duration 6 months; N=111 [259]) or in effects of conventional versus probiotic yogurts [260]; the latter a meta-analysis of 7 parallel-group RCTs (duration 30 days to 12 weeks; N=306 total participants). There also appears no evidence that milk, cheese or butter specifically associate with a risk of T2DM [255], although yogurt and total dairy intakes have been consistently linked with small reductions in rates of T2DM incidence (adjusted summary HR: 0.94 [95%CI: 0.91, 0.98] per 50g/day yogurt and 0.96 [0.94, 0.99] per 200g/day total dairy) [255].

2.7.2.5 Fruits and vegetables

The high emphasis on increasing fruit and vegetable intakes in T2DM dietary guidelines is based on their associations with a variety of favourable health outcomes and their low intakes observed in the general population. Health benefits associated with Mediterranean and DASH dietary patterns are in part ascribed to their emphasis on fruits and vegetables, although specific metabolic contributions of individual fruit and vegetable groups are as yet undetermined [261]. The effects of fruit and vegetables on longer-term glycaemia in T2DM are inconclusive, with very little good-quality trial evidence able to isolate the effects of either. In isocaloric substitution trials from 6-weeks to 6-months duration, not all of which were randomised, comparison arms differed by the amount of fruit (*advised* to be) consumed [262, 263] or by fruit/placebo supplementation [264–266]. Higher-

fruit intakes were generally seen to lead to reduced HbA1c concentrations, but background dietary intakes/changes were unreported, making it difficult to assess isolated effects. A Cochrane review of sweet potato supplementation and its effects on glycaemic control in T2DM also highlighted that all included trials were of very low quality and that changes to HbA1c related to sweet potato were inconclusive [267].

Associations between fruit and vegetable intakes and risk of T2DM is mixed, with no evidence found linking total vegetable or fruit intakes (moderate quality of evidence as assessed through the AMSTAR tool; a measurement tool for assessing methodological quality of systematic reviews [268]) in an umbrella dose-response meta-analysis by Neuenschwander et al [255]. Reduced incidence of T2DM did however associate with greater yellow vegetables, berry fruits, apples and pears intakes (low quality evidence) [255].

2.7.2.6 Legumes

Legumes have been shown to attenuate PPG levels in both those with and without T2DM. This is considered related to their relatively high fibre, amylose to amylopectin starch ratio and possible protein-starch interactions that delay glycaemic absorption [269–271]. A recent meta-analysis of 6 acute-response RCTs (N=68) in people with T2DM, found that PPG was reduced with legume versus control food intakes (varying from wholemeal bread, potato or rice) (MD: -2.90 [95%CI: -4.60, -1.21] mmol/L) (Hafiz et al, 2022). An accompanying meta-analysis of 12 short-term RCTs (duration 3-16 weeks; N=837) also found increased legume intakes were linked with reductions in FPG (MD: -0.54 [-0.83, -0.24] mmol/L), HbA1c (-1.9 [-3.6, -0.0] mmol/mol (-0.17 [-0.33, -0.00] %)) and HOMA-IR (-0.47 [-1.25, -0.31]) (Hafiz et al, 2022). However, results from individual studies in these meta-analyses were highly heterogeneous (I^2=78-93%) and evidence was graded low to very-low quality overall largely as a result of this (Hafiz et al, 2022). The longest of the included studies (16 weeks) provided intervention group participants (n=38) with a legume powder-containing wholegrain-based breakfast and were instructed to otherwise follow their usual diet [272]. The control group (n=38) followed their usual diet. Background diets thus had scope to vary widely between groups in this particular study. Although differences in mean energy intakes and BMI were not deemed significant, they did move in opposite directions on average (reducing in the intervention group but increasing in the usual diet group) [272]. More appropriately-designed RCTs thus remain necessary in this area. From observational research, legume consumption has not been found to associate with T2DM incidence [254, 255].

2.7.2.7 Wholegrains and refined grains

Wholegrains are cereal foods in which the bran, germ and endosperm are intact. In a recent meta-analysis of the effects of wholegrains on glycaemia, sub-group analysis in people with T2DM (9 RCTs of duration 30 days to 1 year 30 days; N=770) indicated reductions occurred in FPG (Weighted MD: −0.84 [95%CI: −1.29, −0.40] mmol/L), HOMA-IR (−0.42 [−0.80, −0.03]) and HbA1c (-6.3 [-9.6, -2.7] mmol/mol (-0.58 [−0.88, −0.25] %)) when following diets higher in wholegrains [273]. However, heterogeneity of between-study results was again high (I^2=64-87%). Interventions combined within the meta-analysis varied between low-GI replacement wholegrain diets, 'healthy' diets supplemented with varying amounts of oats, comparisons against usual diets, or supplementation of ~50% usual diet with either brown rice or white rice. In addition to differences in trial interventions, background diet reporting was poor in the included studies and had scope to vary widely within both intervention and control groups. Finally, weight change differences between groups were not explored in this meta-analysis [273] and several included trials noted greater weight loss in intervention groups, potentially explaining beneficial results attributed to wholegrain consumption [274, 275].

Wholegrains are however a good source of fibre and other essential nutrients and generally feature highly in all healthy eating guidelines, including for T2DM [20, 21]. An umbrella meta-analysis exploring associations between food groups and T2DM incidence determined there was high-quality evidence (again, by the AMSTAR tool [268]) associating wholegrain intakes of 30g/day and reduced risk of T2DM (adjusted summary HR: 0.87 [0.82, 0.93] from 12 primary studies with 22,267 T2DM cases) [255]. Moderate quality of evidence also associated wheat bran intakes of 10g/day with reduced incidence (adjusted summary HR: 0.79 [0.72, 0.87] from 3 primary studies with 10,507 T2DM cases) and white rice intakes of 1 serving/day with increased incidence (adjusted summary HR: 1.23 [1.15, 1.31] from 7 primary studies with 13,637 T2DM cases) [255]. Although evidence therefore indicates a likely benefit of swapping refined carbohydrate sources with wholegrain alternatives for lowering risk of T2DM, more well-designed RCTs are necessary to establish their specific role in glycaemic management following diagnosis.

2.7.2.8 Potatoes

Seven prospective studies with 18,334 incident T2DM cases were meta-analysed by Schwingshackl et al. (2018b) to assess associations between potato intake and T2DM incidence. Results showed 150g/day boiled/baked/mashed-potatoes was associated with slightly increased risk of T2DM incidence (Relative risk (RR): 1.09 [95%CI: 1.01, 1.18]). Stronger associations (RR: 1.66 [1.43, 1.94]) were however observed for each 150 g/day increase in French-fries consumption. Relationships between French-fries intakes and T2DM incidence may of course be confounded by other unhealthy food choices and lifestyle behaviours. This should be considered a possibility in all assessments of associations between specific foods (or diets) and T2DM incidence or management.

2.7.2.9 Beverages

Limiting SSB consumption is widely recommended for T2DM management due to their consistent links with overweight, obesity, CVD and liver disease [21, 276–278]. Although there is seemingly little trial evidence for the effects of SSBs on glycaemic control in T2DM specifically, they are high-GI, have high sugar/energy content, do not promote satiety and are linked with weight gain [279]. In addition, fructose-sweetened beverages have been linked with increased hepatic lipogenesis and insulin resistance [176, 280]. Direct associations between SSB consumption and T2DM incidence in observational studies is also a consistent finding [254, 255, 281].

Despite having a fairly similar sugar content to SSBs, 100% fruit juice appears to have a neutral effect on T2DM incidence in both prospective studies and RCTs [281, 282], suggesting the effects of overall nutrient content within unsweetened fruit juice may offset any possible harms, provided excess energy intake is avoided [283].

Coffee and tea have both been found to be associated with reduced T2DM incidence in a dose-response manner [284, 285], although no effects of tea on glycaemic outcomes were observed within a recent meta-analysis of 10 short-term RCTs (duration ranging 4-16 weeks; N=608) [286].

Finally, in what appears to be the only meta-analysis of the effects of alcohol on glycaemic control in T2DM in short- (4-24 hours) to medium-term (4-104 weeks) RCTs, no evidence of associations were observed between low or moderate intakes of alcohol (median intake 1.5-2.5 units/day) and HbA1c concentrations [287].

2.7.3 Glycaemic effects of dietary patterns

A consistent theme throughout sections 2.7.1 and 2.7.2 is that changes in one nutrient or food will consequently change many nutrient or food intakes simultaneously; either in absolute or in relative terms. Changes or differences in background diets have typically been inappropriately reported or have varied widely between participants, causing difficulty in separating the effects on glycaemia in T2DM of individual dietary components. Dietary pattern analysis can inherently capture multiple simultaneous changes in dietary intakes, in both quantity and quality, avoiding much of the convoluted effects on glycaemia from studies of single nutrients and/or foods (see section 2.6). However, co-occurring weight loss and insufficient recording or adjustment for glucose-lowering medications in many studies [288] still limits interpretation of diet's independent effects on glycaemia outside of benefits chiefly attributable to weight change. In line with this limited evidence for the superiority of any one dietary approach for glycaemic management in T2DM, current dietary guidelines suggest a number of dietary patterns as being suitable for people with T2DM, including the Mediterranean, DASH and other predominantly plant-based dietary patterns [20, 289]. Of particular relevance to this thesis, very few studies have explored associations between diet and long-term glycaemic deterioration in T2DM [98, 118, 290]. Section 2.7.3.1 focuses on evidence relating to the Mediterranean diet, as this has been the most extensively studied dietary pattern at present. In line with the separation of different approaches to dietary pattern analysis presented in section 2.6.1, subsequent sections review the evidence relating *a priori* and *a posteriori*/hybrid-derived dietary patterns with glycaemia in T2DM.

2.7.3.1 Mediterranean dietary pattern

The Mediterranean dietary pattern is based on the eating habits of populations in (mainly) Greece and Southern Italy in the 1960's [291]. Although study-specific definitions of the Mediterranean diet can be seen to vary [292], its essential food-based components are summarised in Table 2.2.

Table 2.2: Food-based characteristics of the Mediterranean diet [293–295].

High consumption	Low-moderate consumption	Low consumption
Fruits	Fish	Red meat
Vegetables	Poultry	Processed meat
Whole grains	Low-fat dairy	Refined grains
Legumes	Wine (generally with meals)	Added sugars
Olive oil as fat source		Eggs (<4 per week)
Nuts/seeds		

The Mediterranean dietary pattern is notable in that two separate studies involving people with T2DM have indicated potential associations between this eating pattern and a delayed need for initiating glucose-lowering medications [97, 98, 290], suggesting the Mediterranean diet potentially aids with delaying disease progression in T2DM.

In a four-year RCT in Italy by Esposito et al [97], free-living people newly-diagnosed with T2DM were randomised to either a Mediterranean-style diet (<50% energy from carbohydrates, >30% energy from fat; n=108) or an iso-caloric low-fat diet (<30% energy from fat, <10% energy from SFA; n=107) to assess the time until glucose-lowering medications became required [98]. Medications were introduced when HbA1c concentrations remained >53 mmol/mol (>7%) for >3 months. Median time to medications was found to be 2.8 [95%CI: 2.4, 3.2] years in the low-fat diet arm and 4.8 [4.3, 5.2] years in the Mediterranean-style diet arm [98]. Adherence to the diets were assessed via monitoring monthly 3-day food diaries during the 4-year RCT and every 6 months during follow-up, although no measures of adherence were reported. No differences were observed in physical activity or total energy intakes between groups, but cumulative between-group weight differences over the study duration appeared to favour the Mediterranean-style diet (-0.98 [-1.5, -0.4] kg), potentially explaining at least part of the differences seen in glycaemia/medication requirements.

Separately, the five-year Prevención con Dieta Mediterránea (PREDIMED) trial investigated effects on CVD prevention with an *ad libitum* Mediterranean diet supplemented with either extra-virgin olive oil (EVOO) or nuts compared with an *ad libitum* low-fat diet [296]. A secondary analysis in n=1,210 with an unspecified duration of T2DM at baseline by Basterra-Gortari et al. [290] indicated that after a median 3.2 years, the Mediterranean diet supplemented with EVOO (n=447) delayed the need for glucose-lowering medications (adjusted HR: 0.78 [95%CI: 0.62, 0.98]) versus the low-fat diet (n=369) [290]. Dietary intakes were assessed quarterly for adherence to each eating plan by trial dietitians using *a priori* designed screening tools. Urinary and plasma biomarkers for EVOO and nut intakes were collected also [297]. However, no differences in time to medication requirement were

found for the Mediterranean diet supplemented with nuts (n=394) compared to the low-fat diet, and no differences between diets were found in the time to initiating insulin (n=3,230; the latter tested in a larger sample containing those already on glucose-lowering medications at baseline) [290]. Weight change differences between groups within the analysis sample were left unexplored, again leaving the independent effects of dietary pattern on glycaemic deterioration unclear. Of key note however when interpreting results derived using data from the PREDIMED study, is that auditing of trial procedures post-trial identified systematic deviations had occurred from PREDIMED randomisation protocols, affecting 21% of trial participants [298]. Specifically, deviations related to non-randomised enrolment of household members, group-level randomisation based on clinic site rather than at the individual-level, and also inconsistent use of randomisation tables [299]. In the secondary analysis by Basterra-Gortari et al. discussed above [290], analyses were performed on an intention-to-treat basis, with potential clustering of participant data due to incomplete randomisation taken into account through model adjustment for baseline variables, propensity scores reflecting probability of assignment to each trial arm, robust variance estimation and rerunning models with all affected participants removed (n=197 and n=476 removed in models exploring time-to-medication initiation and time-to-insulin respectively). Removal of affected participants did not affect study findings but caution needs to be exercised given reservations around PREDIMED data quality.

A network meta-analysis of 56 RCTs by Schwingshackl et al [193] (which included the four-year RCT by Esposito et al [97] described above) compared 9 dietary approaches for their efficacy in achieving glycaemic control in T2DM (durations ranging 3 months to 4 years; N=4,937). All dietary approaches were found to reduce HbA1c compared with control diets which varied from low-fat, 'standard dietary advice', to no intervention. Sub-group analyses indicated that low-carbohydrate diets were most effective for reducing HbA1c over the short-term (<12-months), as observed by other meta-analyses (see section 2.7.1.1.3), as well as in patients aged ≥60 years, whilst Mediterranean diets were most effective over the longer term (≥12-months) and in patients aged <60 years. However, sensitivity analyses indicated that reductions in HbA1c between dietary approaches were associated with differences in weight change, indicating effects were potentially mediated through weight loss rather than any specific dietary approach. Medication use and intervention adherence were also not explored or accounted for in the meta-analysis. Nevertheless, the Mediterranean dietary pattern remains a potential candidate dietary pattern for potentially delaying disease progression in T2DM. A number of other meta-analyses of RCTs have also demonstrated the Mediterranean diet's ability to aid glycaemic control in studies ≥6 months duration, with clinically significant reductions on the

order of 0.30-0.47% (up to 5 mmol/mol) compared to control diets (ranging from low-fat diets, 'diets based on American Diabetes Association eating guidelines' [300], to 'usual care') [188, 301, 302].

2.7.3.2 *A priori* dietary patterns

Potential advantages and disadvantages of dietary pattern assessment via *a priori* methods are discussed briefly in section 2.6.1.1. Only one study could be found attempting to explore associations between a 'dietary pattern' and the rate of glycaemic deterioration in T2DM. In the three-year DIRECT 2.2 observational study (n=625 participants recently-diagnosed with T2DM; see Chapter 6), an *a priori* dietary index score assessing adherence to select components of UK healthy eating guidelines (namely total carbohydrate, sugar, fat, SFA, salt, dietary fibre, fruit and vegetable intakes and total fish intake) [303], did not associate with glucose-lowering medication and BMI-adjusted rates of glycaemic progression (HbA1c deterioration) [118]. However, diet was assessed at baseline only using data from a single 24-hour food record, and pattern scores reflected overall nutrient intakes rather than combined assessment or differentiation of multiple food and nutrient intakes.

Elsewhere in the literature pertaining to T2DM, *a priori* dietary pattern indices/scores have been mostly used to assess associations with incidence of T2DM, rather than exploring associations with glycaemia post-diagnosis. A number of 'healthy' dietary patterns measured via diet screening tools have indeed been linked with reduced incidence of T2DM. The research group of Schwingshackl et al have performed (and updated) a number of systematic reviews and meta-analyses of prospective studies that assess associations between T2DM incidence and dietary patterns measured via the Healthy Eating Index (HEI), Alternate Healthy Eating Index (AHEI) and the DASH score [304–306]. HEI, AHEI and DASH indices generally score diets higher for increased fruit, vegetable, whole grain, nut and legume, low-fat dairy and PUFA intakes, and lower for refined grain, red and processed meat, sodium, SSB, SFA and alcohol intakes [305]. Diets found to score highly against these indices were associated with significant risk reduction for T2DM (RR: 0.81 [95%CI: 0.78, 0.85]; I^2=76%; 16 cohorts), with credibility of evidence graded as 'moderate' using the NUTRIGRADE tool [306, 307]. Additionally, and in line with apparent benefits to aiding glycaemic control post-diagnosis (section 2.7.3.1), a recent meta-analysis of 14 prospective cohort studies (N=410,303; T2DM cases=41,466) found that the highest versus lowest adherers to a Mediterranean dietary pattern (scored via various *a priori* screening tools) had an overall reduced risk of T2DM (RR=0.86 [0.82, 0.91]) [308]. Although between-study heterogeneity was high (I^2=86%) in this meta-analysis, a different meta-analysis by

Jannasch et al [167] suffered from far lower between-study heterogeneity (I^2=26%) and found an almost identical result (RR: 0.87 [0.82, 0.93]).

2.7.3.3 Data driven *a posteriori*/hybrid dietary patterns

Only one study investigating associations between data-driven dietary patterns and glycaemic management in subjects with T2DM could be found within the present literature. In a cross-sectional analysis of 196 Canadian adults with T2DM, Mathe et al [309] derived three dietary patterns via PCA using data from a validated 55-item semi-quantitative FFQ, and explored associations with HbA1c. Patterns were named based on their highest factor loadings ('fried foods, cakes and ice-cream', 'fish and vegetables', 'pasta, potatoes and breads'), but no associations were found between any of the dietary pattern scores and HbA1c concentrations.

Considerably more evidence exists regarding associations between data-driven dietary patterns and incidence of T2DM. Jannasch et al [167] performed a systematic review and meta-analysis of dietary patterns assessed or derived through different methods on T2DM incidence in prospective studies. As mentioned in section 2.6.1.2, comparing data-driven dietary patterns between studies is complicated by, in part, the discordant food groupings used to characterise these patterns. Fourteen studies applying PCA or factor analysis were found to differ in methods of dietary assessment and in the number of dietary predictor variables used (for example, 20 food groupings [310] to 165 food items [311]). Derived patterns were labelled 'prudent' and/or 'Western', but compositions differed. The authors thus evaluated similarities between individual component food groups, identifying two overall groups of patterns; a 'mainly-healthy' pattern characterised by vegetables, legumes, fruits, poultry and fish, and a 'mainly-unhealthy' pattern characterised by refined grains, high-fat dairy, eggs, red and processed meat, and French fries [167]. 'Mainly healthy' patterns were meta-analysed and shown to be associated with a T2DM risk reduction between extreme pattern score quintiles (RR: 0.84 [95%CI: 0.77, 0.91]; I^2=6%) and 'mainly unhealthy' patterns with a T2DM risk increase between extreme pattern score quintiles (RR: 1.44 [1.27, 1.62]; I^2=0%). Relative risks associated with the 'mainly-healthy' dietary patterns are in general agreement with evidence from *a priori* HEI, AHEI and DASH scores analyses (section 2.7.3.2). As alluded to however, meta-analysing data-driven dietary patterns from different populations could be misleading unless patterns have sufficient structural similarity to be classed as equal constructs.

The vast majority of studies exploring associations with T2DM incidence and dietary patterns derived through RRR have used biomarkers as the RRR intermediate responses. Limitations of choosing biomarker responses in RRR are described in section 2.6.1.3.1. There have been multiple combinations of biomarkers used, most of which have been related to inflammatory pathways [161, 166, 312–315]. Several of these dietary patterns [161, 166, 312] were separately replicated through confirmatory-RRR in independent cohorts [161, 313, 316] and subsequently meta-analysed separately by Jannasch et al [167], as described above. RRR patterns explaining variation in HbA1c, HDL-cholesterol, C-Reactive Protein (CRP) and Adiponectin biomarkers were associated with reduced T2DM incidence (RR between extreme quantiles: 0.51 [0.27, 0.98]; I^2=86%). RRR patterns based on explaining variation in purely inflammatory biomarkers (CRP, IL-6, sTNFαR2, E-selectin, sICAM-1, and sVCAM-1) were associated with T2DM incidence (RR between extreme quantiles: 2.53 [1.56, 4.10]; I^2=94%) as were RRR patterns based on HOMA-IR only (RR between extreme quantiles: 1.39 [1.25, 1.54]; I^2=0%). All studies found associations between increased T2DM incidence and the derived patterns, all of which were generally high in refined grains, processed meat, SSBs, and wine; in line with that found from PCA-derived pattern analyses.

Dietary patterns derived through RRR using nutrient intermediate responses typically capture greater levels of response variation compared to when using biomarker intermediate responses, potentially resulting in more informative dietary patterns (see section 2.6.1.3.1). However, only three studies were identified in the current T2DM-relevant literature that used nutrients as RRR responses; all of which explored for associations with T2DM incidence [29, 317, 318]. Hoffmann et al [29] used PUFA to SFA ratio, fibre, magnesium and alcohol intakes as RRR responses in their analysis of the EPIC-Potsdam cohort [319]. Diet was measured once using a 148-item FFQ and T2DM incidence was assessed over a follow-up of 2-3 years in participants aged 35-65 years (193 cases, 385 controls). Data from the FFQ was collapsed into 49 food groups and out of four extracted dietary patterns, the fourth pattern explaining only 3.2% response variation (0.2% variation in PUFA to SFA ratio, 4.4% in fibre, 6.1% in magnesium, 2.0% in alcohol) was found to be associated with T2DM incidence (RR: 0.68 [0.54, 0.85]). Dairy products, coffee, fruit juice, margarine and processed meat all had negative score coefficients (positive effects on T2DM incidence), whilst whole grain bread, fresh fruit, wine and spirits had positive score coefficients (negative effects on T2DM incidence).

Pastorino et al [317] used fibre, GI, and total fat intakes as RRR nutrient responses during analysis of the UK National Survey of Health and Development cohort, using data from multiple 5-day food diaries (at age 36, 43 and 53). Food data was collapsed into 45 food groups with higher pattern scores characterised by higher intakes of processed meat, animal fats, white bread and fried

potatoes and lower intakes of low-fat dairy, fruit, vegetables and wholegrains. This 'high-fat, high-GI, low-fibre' dietary pattern associated with T2DM incidence in middle-aged women only (odds ratio in highest pattern score quintile at age 43: 5.45 [95%CI: 2.01, 14.79]), independent of changes in BMI or waist circumference and proposed to be related to metabolic differences between sexes during peri-menopausal years.

Finally, Brayner et al [318] used SFA, MUFA and PUFA intakes as RRR responses in their recent analysis of UK Biobank [320] participants. The study used dietary data collected from an online hybrid 24-hr recall/FFQ [321], measured across two to five timepoints over ~3 years and then averaged, with food data subsequently collapsed into 48 food groups. Neither a dietary pattern with scores correlating positively with intakes of SFA, MUFA and PUFA ('DP1'; explaining 41% variation in combined fat intakes), nor a dietary pattern correlating positively with SFA and negatively with PUFA ('DP2'; explaining 24% variation in combined fat intakes) associated with incidence of T2DM during an average 6.3 years follow-up [318]. Higher DP1 scores corresponded with greater intakes of nuts and seeds, vegetable dishes, butter, eggs, and sweet baked foods, and lower intakes of fruits, low-fat yogurt, and wine. Higher DP2 scores corresponded with greater intakes of butter, high-fat cheese, ice cream, beef and sweet baked foods, and lower intakes of nuts and seeds, vegetables and margarine. Given the dietary pattern scores were limited to maximising differences in intakes of fat quality only, the lack of association with T2DM incidence is perhaps due to the multifactorial nature of T2DM and the lack of variation in other nutrient or food intakes potentially relevant in T2DM incidence or subsequent management (see sections 2.7.1 and 2.7.2).

2.8 Dietary patterns in men and women

Dietary patterns are typically found to differ between men and women [31, 32]. In years 1 to 4 (2008–2012) of the UK National Diet and Nutrition Survey (NDNS), dietary patterns derived through principal component analysis (PCA; see section 2.6.1.2.1) revealed that men reported following dietary patterns higher in meats, sugary foods, fried foods and refined grains and lower in fruits and vegetables compared to women [31]. Such trends are seen globally, with men reporting following diets higher in unhealthy foods and lower in unhealthy foods compared with women [32]. For men and women with T2DM however, evidence is generally lacking for what typical dietary patterns look like. Importantly, it is unknown how dietary patterns change in each sex separately following typical, patient-centred dietetic advice (section 2.3), as results from intervention studies are typically

reported for both sexes combined. Multiple differences have however been observed to exist between men and women in their typical attitudes and behaviours relating to food; a result of both biology [33] and gender social norms [34]. Chapter 4 explores these issues and the evidence surrounding them in greater detail and seeks to determine whether men and women with T2DM potentially require a more divergent dietetic approach for promoting dietary pattern change.

2.9 Summary

T2DM is a progressive disease, manifesting clinically through ongoing glycaemic deterioration despite escalating medication use. The rate of disease progression is however found to be highly heterogenous amongst individuals. There is a significant lack of long-term studies assessing the effects of diet on long-term glycaemia, and likewise, on rates of glycaemic deterioration in T2DM. Diet remains a cornerstone of treatment and weight loss is universally advocated for improving glycaemic control. Whether dietary intakes benefit glycaemia independent to the effects of weight loss, however, remains unclear. Although this issue may appear largely academic given clinical focus should be on achieving long-term glycaemic control for patients, regardless of mechanism, understanding potential mechanisms of action of diet on glycaemia may aid with provision of appropriate advice to patients and in turn reduce diet-related anxieties that may be present. It is however difficult to attribute effects on glycaemia to single dietary components as there is inevitably confounding by differences or changes elsewhere in the diet. It is likely that the combined effects of multiple nutrients and foods are key for appropriate T2DM management, something which dietary pattern analysis is able to capture as a single construct. There appears some evidence that the Mediterranean dietary pattern associates with a delayed need for glucose-lowering medications in T2DM, potentially as a result of induced weight loss, although this remains unclear. However, evidence indicates that the Mediterranean diet is not followed to a great degree by people within the UK [295], and scoring prospective dietary data for adherence to this pattern using an a priori index is therefore unlikely to capture significant dietary variation, nor the specific variation in diet perhaps most relevant to glycaemia. Data-driven, hybrid dietary pattern techniques such as reduced-rank regression can be used to derive dietary patterns that act through theoretical nutrient-disease pathways, potentially maximising causal inference relating combined nutrient and food intakes with glycaemia.

Many other issues prevent firm conclusions being made regarding the effects of diet on glycaemia in T2DM, from inappropriate reporting or adjustment for glucose-lowering medications, to poor

adherence rates to dietary interventions. Resolving such issues are key for reaching conclusions for the effects of diet in T2DM. Observational analyses of prospective diet data during and following a dietary intervention can theoretically avoid issues related to poor dietary adherence, in turn providing an indication of what dietary changes may be achievable under 'real-world' conditions and dietetic care. In turn, given health disparities and the known differences in typical dietary intakes and diet-related behaviours observed between men and women, the exploration of dietary pattern changes by sex following a patient-centred dietary intervention could be important for bridging any gap in health inequalities.

The aim of this thesis is to explore relationships between nutrient-mediated dietary patterns and changes in glycaemia in early type 2 diabetes. This will cover relationships over the shorter-term during a large 12-month dietary intervention (described in more detail within section 3.3.2), whereby effects independent of weight change will be explored (Study 1). Study 2 follows by exploring short- and longer-term dietary pattern change during and following a non-prescriptive, patient-centred dietary intervention in men and women to assess whether such interventions produce similar dietary pattern change in both. Study 3 assesses relationships that may exist between nutrient-mediated dietary patterns and the rate of change in glycaemia over the longer-term. Finally, study 4 aims to replicate analyses from study 3 in a larger, more diverse cohort. As stated within the thesis introduction, this will aim to answer the following research questions:

1) Do changes in nutrient-mediated dietary patterns associate with short-term glycaemic control independent of the effects of weight change in early type 2 diabetes?
2) During and following a non-prescriptive, patient-centred dietary intervention in early type 2 diabetes, do dietary pattern changes diverge between men and women?
3) Do nutrient-mediated dietary patterns associate with longer-term glycaemic progression in early type 2 diabetes?
4) Are associations between nutrient-mediated dietary patterns and longer-term glycaemic progression in early type 2 diabetes replicable and generalisable between cohorts?

Chapter 3 - Study 1: Is glycaemic control associated with dietary patterns independent of weight change in people newly diagnosed with type 2 diabetes? Prospective analysis of the Early-ACTivity-In-Diabetes trial.[1]

3.1 Abstract

Background: It is unclear whether diet affects glycaemic control in type 2 diabetes (T2D), over and above its effects on bodyweight. We aimed to assess whether changes in dietary patterns altered glycaemic control independently of effects on bodyweight in newly diagnosed T2D.

Methods: We used data from 4-day food diaries, HbA1c and potential confounders in participants of the Early-ACTivity-In-Diabetes trial measured at 0, 6 and 12 months. At baseline, a 'carb/fat balance' dietary pattern and an 'obesogenic' dietary pattern were derived using reduced-rank regression, based on hypothesised nutrient-mediated mechanisms linking dietary intake to glycaemia directly or via obesity. Relationships between 0-6 month change in dietary pattern scores and baseline-adjusted HbA1c at 6 months (n=242; primary outcome), were assessed using multivariable linear regression. Models were repeated for periods 6-12 months and 0-12 months (n=194 and n=214 respectively; secondary outcomes).

Results: Reductions over 0-6 months were observed in mean bodyweight (-2.3 (95%CI: -2.7, -1.8) kg), body mass index (-0.8 (-0.9, -0.6) kg/m^2), energy intake (-788 (-953, -624) kJ/day), and HbA1c (-1.6 (-2.6, -0.6) mmol/mol). Weight loss strongly associated with lower HbA1c at 0-6 months (β=-0.70 [95%CI -0.95, -0.45] mmol/mol/kg lost). Average fat and carbohydrate intakes changed to be more in-line with UK healthy eating guidelines between 0-6 months. Dietary patterns shifting carbohydrate intakes higher and fat intakes lower were characterised by greater consumption of fresh fruit, low-fat milk and boiled/baked potatoes and eating less of higher-fat processed meats, butter/animal fats and red meat. Increases in standardised 'carb/fat balance' dietary pattern score associated with improvements in HbA1c at 6-months independent of weight loss (β=-1.54 [-2.96, -

[1] This study was published as, "Garbutt J, England C, Jones AG, Andrews RC, Salway R and Johnson L. Is glycaemic control associated with dietary patterns independent of weight change in people newly diagnosed with type 2 diabetes? Prospective analysis of the Early-ACTivity-In-Diabetes trial. BMC Medicine. 2022; 20:161. DOI: 10.1186/s12916-022-02358-5." The abstract, introduction, results, methods and discussion (sections 3.1 to 3.8) are presented as per the article.

0.13] mmol/mol/SD). No evidence of association with HbA1c was found for this dietary pattern at other time-periods. Decreases in 'obesogenic' dietary pattern score were associated with weight loss (β=-0.77 [-1.31, -0.23] kg/SD) but not independently with HbA1c during any period.
Conclusions: Promoting weight loss should remain the primary nutritional strategy for improving glycaemic control in early T2D. However, improving dietary patterns to bring carbohydrate and fat intakes closer to UK guidelines may provide small, additional improvements in glycaemic control.
Trial registration: ISRCTN92162869. Retrospectively registered on 25th July 2005.

3.2 Background

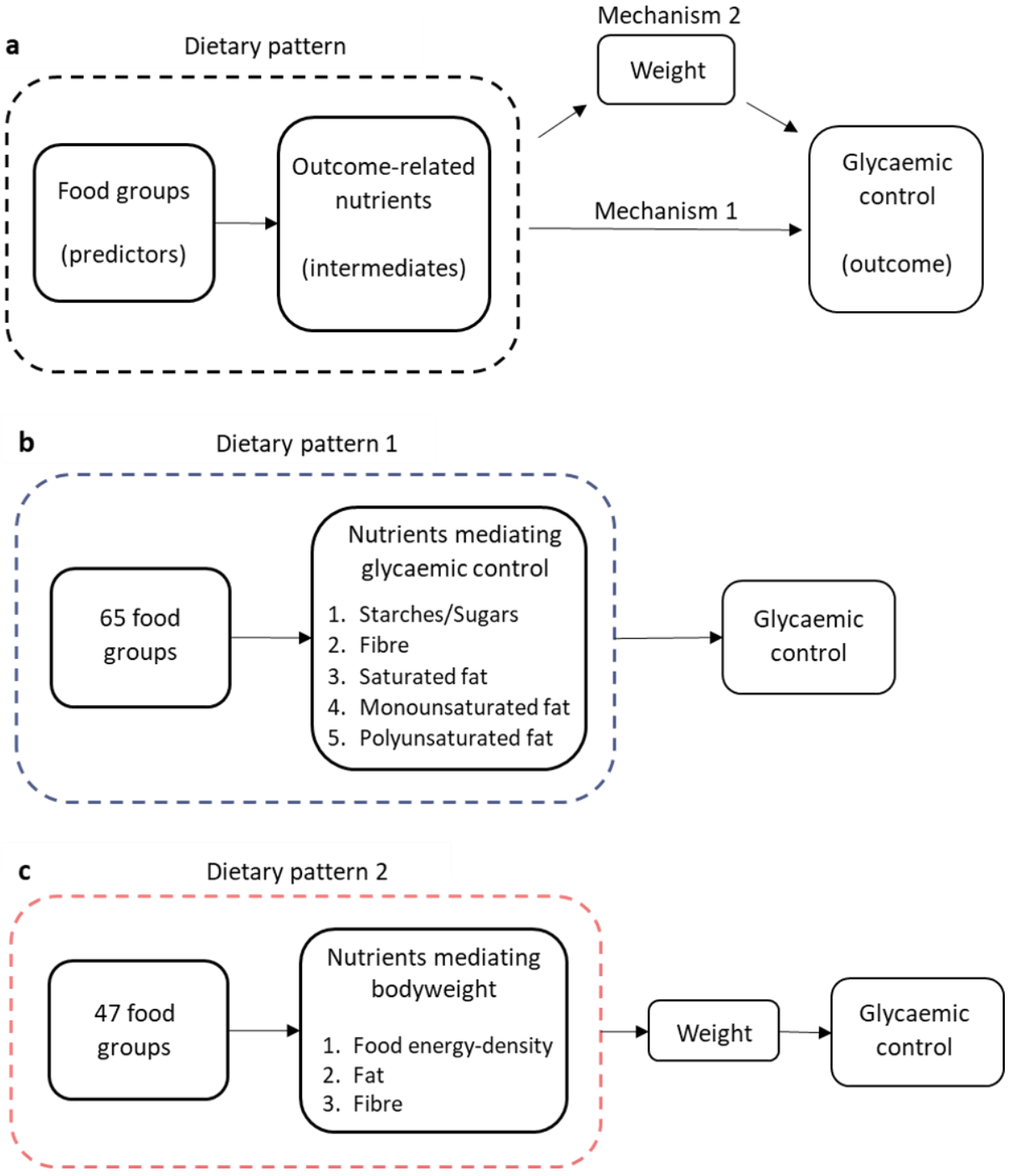
Diet is one of the cornerstones of treatment for patients diagnosed with type 2 diabetes [20, 23]. Nutritional guidelines for glycaemic management focus on individualised recommendations rather than specifying a "one-size-fits-all" approach [20, 23]. Improved HbA1c concentrations are consistently associated with weight-loss through caloric deficit achieved by a range of specific dietary changes [22, 70]. However, it remains unclear if specific dietary patterns can offer further benefits to glycaemic control beyond their effect on bodyweight.

Evidence for appropriate dietary intakes in type 2 diabetes, notably relating to carbohydrates, is inconsistent [192, 288]. Separating potential effects of dietary composition change from the known effects of weight change on glycaemic control is difficult as both typically co-occur. Dietary trials in type 2 diabetes have also tended to focus on manipulating intakes of only single nutrients, such as comparing "low-carb" vs "high-carb" diets, but this bears little resemblance to real-world eating behaviours. People eat foods comprising of multiple nutrients. Changing food intakes to modify one nutrient inevitably changes many nutrient intakes simultaneously. Capturing these multiple dietary changes in the form of a 'dietary pattern', alongside an understanding of the mechanisms through which these might act, is key for appreciating any specific effects of diet in type 2 diabetes.

Reduced-rank regression (RRR) is an analytical technique that identifies dietary patterns in reported food intakes by combining existing knowledge and theory of diet-disease mechanisms with data-driven analysis of real-world eating behaviours [29]. RRR can establish the relative importance of different nutrient-mediated mechanisms potentially linking diet directly to glycaemic control or indirectly via weight loss (see Figure 3.1a-c). Identifying key foods that explain the most variation in these specific diet-disease mechanisms may in turn offer high-priority food targets for dietetic management of type 2 diabetes, therefore offering significant clinical potential.

Figure 3.1: Changes in dietary patterns constructed to explain differences in intakes of multiple nutrients simultaneously are explored for independent (mechanism 1) and weight-dependent (mechanism 2) associations with changes in glycaemic control.

a: General pathway diagram; *b*: Mechanism 1 - dietary pattern 1 hypothesised to directly associate with glycaemic control; *c*: Mechanism 2 - dietary pattern 2 hypothesised to indirectly associate with glycaemic control via effects on bodyweight.



To our knowledge, no study has applied RRR to identify dietary patterns associated with glycaemic control in patients with type 2 diabetes. However, RRR has been applied to derive dietary patterns associated with type 2 diabetes incidence [29, 161, 312, 313, 317, 322]. Reduced incidence has generally been associated with dietary patterns high in wholegrains and vegetables and low in refined-grains, sugar-sweetened beverages and processed meats. In the majority of these studies, inflammatory biomarkers were used as the intermediate mechanisms linking food intake with type 2 diabetes, rather than nutrients. Inflammatory biomarkers are subject to multiple influences beyond dietary patterns and therefore may not capture the dietary variation most relevant to type 2 diabetes compared with using nutrient intermediates [167]. Associations between biomarker-mediated dietary patterns and type 2 diabetes incidence are also potentially self-fulfilling, as the intermediate biomarkers used in the dietary pattern's construction associate with incidence *a priori*. Instead, nutrients as potential diet-disease intermediates will be more proximal to dietary intakes, and should only produce self-fulfilling associations in as far as the chosen nutrients are true mediators between diet and disease.

The nutritional changes hypothesised to optimise glycaemic control may differ from the nutritional changes required to optimise weight loss. For instance, several nutrients potentially directly link diet with glycaemic control ('mechanism 1'); fibre moderates post-prandial blood glucose excursions caused by starchy and sugary carbohydrate consumption, while replacing saturated with unsaturated fats has been observed to benefit insulin sensitivity [28, 180, 323]. Several other nutrient factors have the potential to link diet to glycaemic control via their effects on bodyweight ('mechanism 2'), such as dietary energy-density and chief calorie contributors and appetite buffers like total fat and fibre [324, 325] (Figure 3.1a-c). Understanding the effects of simultaneous changes in these nutrients in the form of a dietary pattern, as derived using RRR, allows exploration of these nutrients' combined importance in their potential impact on glycaemic control.

In this study, we investigate whether changes in dietary patterns that explore nutrient-mediated disease mechanisms were independently associated with changes in HbA1c observed over 6- or 12-months of the Early-ACTivity-In-Diabetes (Early-ACTID) trial **[ISRCTN Registry: 92162869]** [326].

3.3 Methods

3.3.1 Sample

Data came from the Early-ACTID trial [326, 327], a 12-month, multi-centre, parallel-group randomised controlled trial involving 593 adults diagnosed in the previous 5-8 months with type 2 diabetes. Recruitment took place from December 2005 to September 2008 within South-West England. Participants were randomised to either a usual care, dietary intervention or diet and physical activity intervention group. During the first 6 months of the study, glucose-lowering medications were not changed. Trial endpoints were HbA1c and blood pressure at 6-months (primary) and 12-months (secondary) post-intervention. The study was approved by the Bath Research Ethics Committee (05/Q2001/5), and all participants provided written informed consent.

3.3.2 Intervention

Usual care consisted of standard dietary and exercise advice at 0 and 12-months, with an interim review by study doctors and nurses at 6-months, where no further advice was given. The diet intervention aimed to enable and maintain 5–10% weight loss through a non-prescriptive dietary intervention based on 2003 Diabetes UK nutrition guidelines [328] and UK Food Standards Agency's 'Balance of Good Health' [329]. Specifically, participants were encouraged to base meals on starchy carbohydrates and choose higher-fibre/wholegrain options, reduce added sugars, increase oily fish and reduce fatty and processed meat intakes, and choose lower-GI and energy-density foods. Guidance also included maintaining a regular meal pattern alongside general portion-size control. Dietitians met with participants at randomisation and every 3-4 months, with study nurses reinforcing advice every 6-weeks. The diet and physical activity intervention consisted of the same dietary intervention as the diet-only group. Participants were however advised to do an additional ≥30 minute walk on ≥5 days per week. Study nurses also discussed physical activity during the 6-weekly appointments. Total contact time was the same in both intervention groups.

3.3.3 Dietary data

Diet was self-reported using 4-day food diaries covering two weekdays and two weekend days. All foods and drinks (including alcohol) were reported with estimated portion sizes using household measures or package weights, noting brands and cooking methods where appropriate. Food diaries were coded according to the University of Bristol's Centre for Exercise, Nutrition and Health Sciences

food diary codebook. This codebook is based on the INTERMAP study [330]; common foods in the first six years (2008-2014) of the UK National Diet and Nutrition Survey (NDNS) [331]; portion sizes from the 2006 *Final Technical Report to the Food Standards Agency on Typical Food Portion Sizes in Adults* [332]; and coding rules taken from the UK ALSPAC [333] and AIRWAVE [334] study codebooks.

Food diaries were coded by two researchers and quality-checked by two others in line with best practise for minimising coding errors [330]. *Diet In Data Out* nutritional analysis software [335] was used for analysing 0 and 6-month diaries and *DietPlan* (v7; Forestfield Software Limited, UK) was used for 12-month diaries. Diet analyses used nutrient data published in the 2002 UK *Composition of Foods Integrated Dataset* (COFID) [336] to more closely match food composition at the time of the trial, or if missing, the updated 2015 COFID database [337].

3.3.4 Diet pattern derivation

Average daily percentage total energy intake (TEI) were calculated using updated Atwater factors [338] for starches and sugars combined, saturated fats (SFA), monounsaturated fats (MUFA), polyunsaturated fats (PUFA) and total fat intakes using: 100*energy from nutrient (kJ)/total energy (kJ). Average daily fibre-density was calculated using total fibre (g)/total energy (MJ). Average daily dietary energy-density (DED) was calculated using total food energy (kJ)/total food weight (g); excluding drinks to prevent inappropriately diluting estimates [339].

All dietary patterns were derived using RRR**.** Fibre-density (g/MJ) and percentage energy from starches and sugars, SFA, MUFA, and PUFA (%TEI) were used as intermediate variables for deriving a dietary pattern based on evidence that individual macronutrients directly affect glycaemia [28, 180, 323] (mechanism 1; Figure 3.1b). DED (kJ/g), total fat (%TEI), and fibre-density (g/MJ), were used as intermediate variables for deriving a dietary pattern hypothesised to indirectly associate glycaemic control via bodyweight (mechanism 2; Figure 3.1c), replicating previous methods [324, 325, 340, 341]. For dietary pattern mechanism 1, food items were allocated to 65 groups based on culinary usage and to maximise differences in fat and carbohydrate quality (Table S8.1). For dietary pattern mechanism 2, 47 food groupings based on previous studies were used [325] (Table S8.1). Average intake of each food group was calculated in g/day at 0, 6 and 12-months for each participant.

RRR derives a dietary pattern score for each participant computed from their individual standardised food group intakes weighted by dietary pattern loadings derived at group-level. Pattern scores are increased when participants report eating more of food groups with higher (positive) pattern loadings or eating less of food groups with lower (negative) pattern loadings. RRR produces as many dietary patterns as intermediate variables used; hence, for dietary pattern mechanism 1 this was 5, and for dietary pattern mechanism 2 this was 3 patterns. To identify a single score for each pattern that captured the combination of food groups explaining most variation in specified nutrient intermediates, we only retained the first patterns for subsequent analyses. To confirm whether the pattern structures (i.e. the size or direction of food group loadings for pattern scores) changed over time, we repeated the RRR independently at 6 and 12-months and compared the first patterns derived at these timepoints with the first patterns at baseline using Tucker's congruence coefficient (CC) [342]. After confirming patterns were similar (CC>0.85), food group pattern loadings at baseline were used to compute dietary pattern scores at 6 and 12-months, thus allowing changes in adherence to the same dietary pattern structure to be measured. We also assessed congruence between dietary pattern 2 and dietary patterns derived using identical methods in the UK NDNS [325], to assess stability of this pattern between populations.

3.3.5 Misreporting of energy intake

Dietary misreporting at baseline was assessed via an individualised method [143] using a ratio of reported energy intake to estimated energy requirement, calculated from standard equations [343] (Information S8.1 [344, 345]). Assuming energy balance, energy intake is expected to be equal to estimated energy requirements. Early-ACTID was a weight-loss trial, so while energy balance may be assumed at baseline it is an unreasonable assumption during the intervention. Therefore, baseline misreporting status was used to assign misreporting status at later timepoints, as misreporting has previously been seen to track within individuals [346]. As few over-reporters were identified (n=4), these were combined with plausible-reporters and a binary categorical variable (under-reporter and plausible-reporter) was used in analyses.

3.3.6 Covariates

Diet, physical activity, anthropometry, medications, clinical and haematological measures including HbA1c were assessed at three timepoints (0-, 6- and 12-months post-randomisation). HbA1c was measured in plasma using HPLC in a single laboratory. Oral hypoglycaemic agents (OHAs), namely metformin, sulphonylureas and glitazones, were recorded by trial clinicians as type and dose. Physical activity was assessed over 7 days via waist-worn, uni-axial accelerometers (*Actigraph GT1M; Actigraph LLC, Pensacola, FL, USA*), with data processing as detailed previously [347]. Participants were additionally scored against the 2007 UK Index of Multiple Deprivation (IMD) based on their home postcode at baseline [348]. Covariates used for analyses were 0, 6, and 12-month percentages of maximum OHA medication dose, average daily total physical activity, bodyweight and TEI, and baseline age, sex and dietary-misreporting status.

3.3.7 Statistical analysis

Variables were described with the use of mean (standard deviation (SD) or 95% confidence interval (95%CI)) if normally distributed or median (quartile 1, quartile 3) otherwise. Associations between participant characteristics and changes in dietary patterns and high pattern loading food groups were explored by describing the sample by quintile of dietary pattern score change. To help understand what a 1-SD change in dietary pattern score means, nutrient intake changes relating to a 1-SD increase in dietary pattern score were calculated using simple linear regression, with dietary pattern score as predictor and either DED, fibre-density or percentage energy from the relevant nutrient as outcomes.

The primary outcome of this study was change in HbA1c over 0-6 months (0-6m), a period when no changes in medications were made and thus diet had the most potential to affect HbA1c. Changes in HbA1c during 6-12 months (6-12m) or 0-12 months (0-12m) were explored as secondary outcomes, adjusting for changes in medications during the latter half of the trial. Trial periods were thus modelled separately to distinguish effects attributable to lifestyle only to that of lifestyle and medications combined.

A series of multivariable linear regressions were used to assess whether dietary pattern changes during 0-6m were associated with glycaemic control, as measured through change in HbA1c. *Model 1* estimated the unadjusted association between each dietary pattern score change (exposure) and HbA1c change using end-of-period (6-month) HbA1c as the outcome, adjusting for start-of-period

(baseline) HbA1c and dietary pattern score. *Model 2* estimated the association independent of potential confounders by adding to model 1, age, sex, misreporting status, and period-change in total physical activity. Model 3 estimated potential mediation by adding period-change in TEI and bodyweight to model 2. To assess the subsequent 6-month and longer-term association between dietary pattern change and HbA1c, we repeated models 1-3 for 6-12m and 0-12m periods. In these models we additionally adjusted for OHA medication change within models 2 and 3. Units of dietary pattern change effect estimates within these models were for an equivalent 1-SD change in baseline dietary pattern score. We considered $p<0.05$ being evidence of association.

3.3.8 Sensitivity Analyses

We ran a series of sensitivity analyses to check our assumptions relating to missing data, linearity of associations, interactions by sex, model adjustment with trial arm and associations between bodyweight and HbA1c change (Information S8.2).

Analyses were performed in *Stata* (v15; StataCorp LLC, College Station, TX, USA), with the RRR procedure incorporating *SAS* (v9; SAS Institute, North Carolina, USA) (Information S8.3).

3.4 Results

3.4.1 Sample characteristics

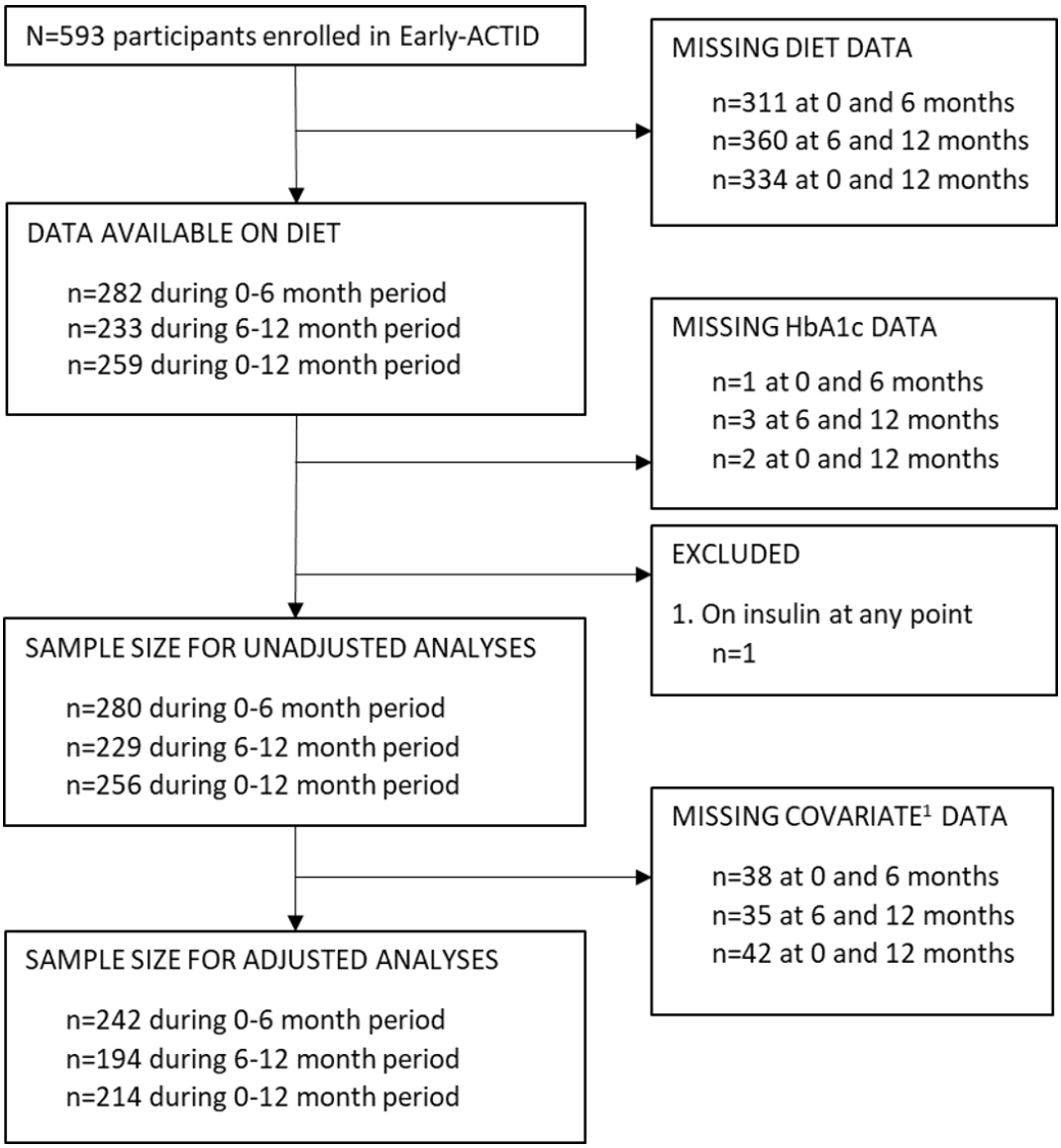
Complete data for our primary analysis between 0-6m was available in n=242 participants (41% of those enrolled at baseline) (Figure 3.2), of which 67% were male with median age 62 years, weight 86.5kg, body mass index (BMI) 29.5kg/m^2 and HbA1c 47 mmol/mol (6.5%) (Table 3.1 and Table 3.2). Baseline characteristics of all trial participants (N=593) and of those included in our secondary analyses (n=194 at 6-12m; n=214 at 0-12m) are shown in Table S8.2. Fewer participants in the secondary analyses came from the usual care group (7% vs. 17%) and were more likely to be male (70-71%) and slightly older (median baseline age 63 years), but were otherwise similar to participants in the 0-6m analyses.

Weight, BMI, TEI and HbA1c changes were larger in the first compared with the last 6 months of the study. Average weight, BMI, TEI and HbA1c all reduced during 0-6m (mean change: -2.3 (95%CI: -2.7, -1.8) kg; -0.8 (-0.9, -0.6) kg/m^2; -788 (-953, -624) kJ; -1.6 (-2.6, -0.6) mmol/mol [-0.15 (-0.24, -0.06)

%]). While average weight and BMI remained the same during 6-12m (0.0 (-0.3, 0.4) kg and 0.0 (-0.1, 0.1) kg/m^2), average TEI and HbA1c reduced further but to a lesser degree (-365 (-547, -184) kJ; -0.4 (-1.4, 0.6) mmol/mol [-0.03 (-0.13, 0.06) %]).

Missing data analysis (Table S8.2) indicated that characteristics of participants in our primary analyses (n=242) differed to the full Early-ACTID cohort (n=593) at baseline by being slightly older (62 vs 61 years), with a lower bodyweight (86.5 vs 89.0 kg) and BMI (29.5 vs 30.4 kg/m2), and lowered bodyweight, BMI and HbA1c to a greater degree during 0-6m (-2.1 vs -1.3 kg; -0.7 vs -0.5 kg/m^2; -2.2 vs -1.1 mmol/mol [-0.2 vs -0.1 %]).

Figure 3.2: Sample size flow chart.



[1] *Covariates were age, sex, bodyweight, energy intake, total physical activity, under-reporting status and metformin, sulphonylurea, and glitazone dose.*

Table 3.1**:** Baseline and 0-6 month change characteristics for n=242 participants with complete data during 0-6 months.

		0-6m participant characteristics (models 1a-3)
n (% full cohort)		242 (41%)
Arm, n (% sample)		
	Usual care	16 (7%)
	Diet	115 (48%)
	Diet & Exercise	111 (46%)
Male, n (%)		163 (67%)
White ethnicity, n (%)		236 (98%)
Smoker at baseline, n (%)		17 (7%)
Age, years		62 (57, 69)
Time since diagnosis, years		0.5 (0.4, 0.6)
IMD score		12.6 (6.4, 18.9)
Total activity, counts/min		291 (226, 363)
Total activity change 0-6m, counts/min		16 (-44, 91)
MVPA, mins/day		21 (13, 36)
MVPA change 0-6m, mins/day		3 (-6, 18)
Weight, kg		86.5 (77.1, 94.0)
Weight change 0-6m, kg		-2.1 (-3.9, -0.1)
BMI, kg/m^2		29.5 (27.3, 32.7)
BMI change 0-6m, kg/m^2		-0.7 (-1.4, 0.0)
HbA1c, mmol/mol		47 (43, 54)
HbA1c, %		6.5 (6.1, 7.1)
HbA1c change 0-6m, mmol/mol		-2.2 (-5.5, 3.3)
HbA1c change 0-6m, %		-0.2 (-0.5, 0.3)
OHA prescription, n (%)		
	Metformin	85 (35%)
	Sulphonylurea	22 (9%)
	Glitazone	2 (1%)
Baseline under-reporters, n (%)		142 (56%)

Data presented as median (quartile 1, quartile 3) or n (%). IMD – index of multiple deprivation; MVPA – moderate-vigorous physical activity; OHA - oral-hypoglycaemic agent.

Table 3.2**:** Baseline and 0-6 month nutrient intake changes in n=242 with complete data during 0-6 months.

Nutrient	Median (Q1, Q3)
Total energy intake, kJ	7377 (6220, 8619)
Total energy intake change 0-6m, kJ	-741 (-1640, -6)
Dietary energy density, kJ/g	6.3 (5.6, 7.1)
Dietary energy density change 0-6m, kJ/g	-0.3 (-1.1, 0.4)
Starches/sugars, %TEI	43.5 (39.6, 48.2)
Starches/sugars change 0-6m, %TEI	0.6 (-3.2, 5.4)
Dietary fibre density, g/MJ	2.3 (1.9, 2.6)
Dietary fibre density change 0-6m, g/MJ	0.1 (-0.2, 0.5)
Total fat, %TEI	33.8 (30.3, 37.0)
Total fat change 0-6m, %TEI	0.1 (-3.8, 3.7)
SFA, %TEI	11.0 (9.4, 13.0)
SFA change 0-6m, %TEI	0.1 (-2.2, 1.8)
MUFA, %TEI	12.1 (10.5, 13.7)
MUFA change 0-6m, %TEI	0.3 (-1.5, 2.0)
PUFA, %TEI	6.5 (5.3, 7.9)
PUFA change 0-6m, %TEI	0.0 (-1.6, 1.6)

Q1 – quartile 1; Q3 – quartile 3; TEI – total energy intake; SFA – saturated fat; MUFA – monounsaturated fat; PUFA – polyunsaturated fat.

3.4.2 Pattern 1 – 'Carb/fat balance' dietary pattern

A 'carb/fat balance' dietary pattern was identified at baseline. Higher pattern scores correlated with higher percentage energy from starches and sugars (r=0.74) and fibre-density (r=0.68), and lower percentage energy from SFA (r=-0.64), MUFA (r=-0.63) and to a lesser extent PUFA (r=-0.12) (Table S8.3 [342]). The dietary pattern score thus represented a contrast in the amounts, but not the quality, of carbohydrate and fat intakes. A higher pattern score associated with eating more 'fruit (fresh)', 'low-fat milk', 'boiled/baked potatoes', and 'legumes', while also eating less 'higher-fat processed meats', 'butter/animal fats', 'red meat', and 'low-fibre bread' (Figure S8.1a). A 1-SD higher 'carb/fat balance' dietary pattern score at baseline equated to consuming 7.0% more energy from carbohydrate (6.6% from combined starches and sugars and 0.5g/MJ more fibre) and -4.9% less energy from fat (-2.6%, -2.0%, -0.3% from SFA, MUFA, and PUFA respectively).

3.4.3 Pattern 2 – 'Obesogenic' dietary pattern

An energy-dense, higher-fat, lower-fibre ('obesogenic') dietary pattern was identified at baseline. Higher scores correlated with higher DED (r=0.81) and percentage energy from fat (r=0.60), and lower fibre-density (r=-0.72) (Table S8.4). A higher pattern score associated with eating more 'low-

fibre bread', 'processed meat', 'coated chicken/fish' and 'fried/roast potatoes/chips', while also eating less 'fruit (fresh)', 'vegetables (raw/boiled/grilled)', 'yoghurts', and 'boiled/baked potatoes' (Figure S8.1b). A 1-SD higher 'obesogenic' dietary pattern score at baseline equated to 1.0 kJ/g higher DED, 3.5% more energy from fat, and 0.4g/MJ less fibre-density. The 'obesogenic' dietary pattern was structurally similar to that previously derived within the UK NDNS (CC=0.88).

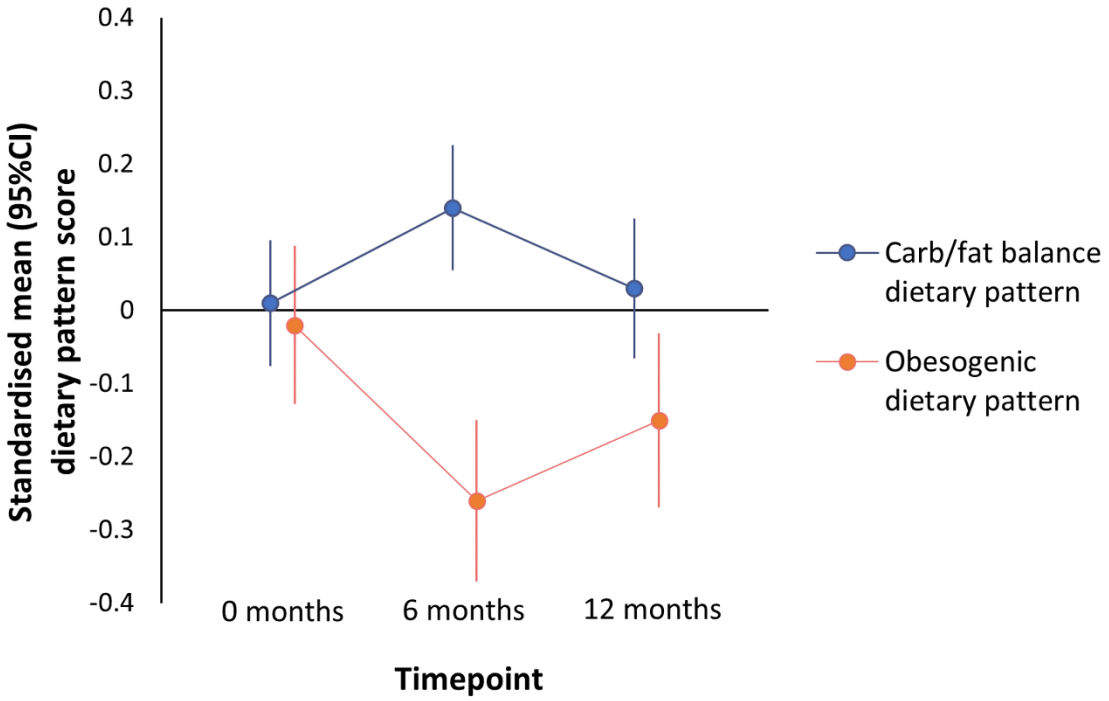
3.4.4 Changes in dietary patterns

During 0-6m (n=242), changes in 'carb/fat balance' dietary pattern scores indicated movement towards intakes slightly higher in carbohydrates and lower in fats (Mean change: 0.12, SD 0.78) (see Figure 3.3). In the same period, changes in 'obesogenic' dietary pattern scores indicated dietary intakes became less energy-dense, lower-fat, and higher-fibre (-0.24, SD 0.94). During 6-12m (n=194), dietary patterns reverted back towards intakes lower in carbohydrates and higher in fats (-0.13, SD 0.81), and to a lesser degree, intakes that were more energy-dense, higher-fat and lower-fibre (0.11, SD 0.96).

Participants who changed their dietary patterns most over 0-6m had greater reductions in TEI, bodyweight and HbA1c, greater increases in total physical activity and daily minutes of moderate-vigorous physical activity, a higher baseline IMD and were taking more OHA medications (Table S8.5-Table S8.6). Those who made the greatest change in 'carb/fat balance' dietary pattern score (Table S8.5 quintile 5) made slightly greater changes in total carbohydrate, fat and SFA intakes than those who made the greatest change in 'obesogenic' dietary pattern score during 0-6m (Table S8.5 quintile 1). Average total carbohydrate, fat and SFA intake in the former at baseline were 41.9%TEI, 36.9%TEI and 12.6%TEI respectively, changing to 49.2%TEI, 32.3%TEI and 10.1%TEI respectively by 6 months.

Figure 3.3: Average standardised diet pattern scores at 0, 6 and 12-months.

Pattern scores are offset to aid visualisation.



3.4.5 Associations between changes in dietary patterns and HbA1c independent of weight changes

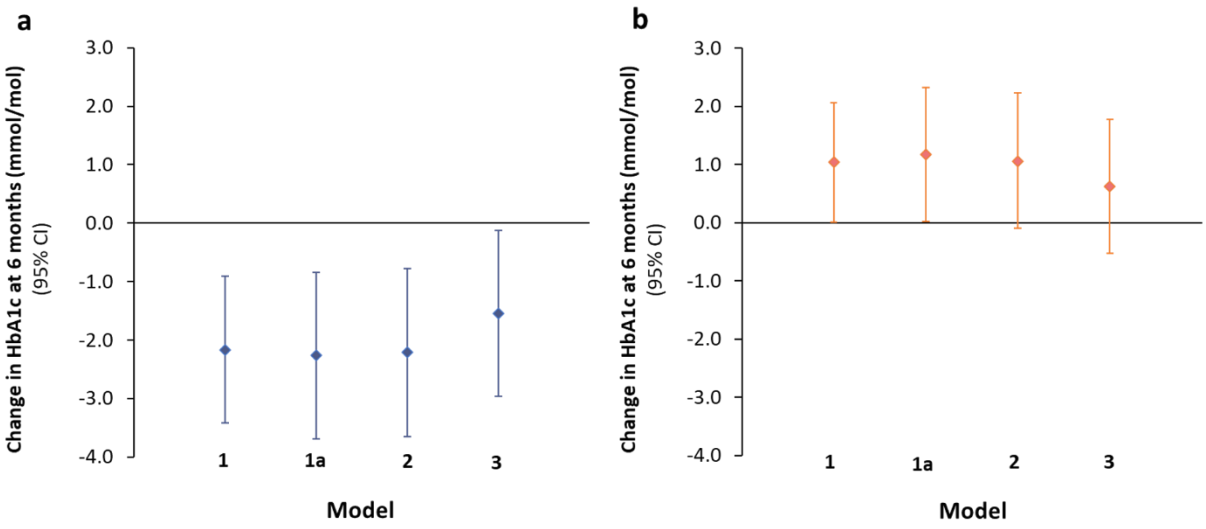
There was strong evidence that increases in 'carb/fat balance' dietary pattern scores were associated with reductions in HbA1c between 0-6m after adjustment for potential confounders (model 2: β=-2.21 [-3.65, -0.78] mmol/mol/SD; *p*=0.003). This association was only partially mediated following further adjustment for bodyweight and TEI change (β=-1.54 [-2.96, -0.13] mmol/mol/SD; *p*=0.033) (Figure 3.4a; Table S8.7).

We found no evidence of association between changes in 'obesogenic' dietary pattern scores and changes in HbA1c after adjustment for potential confounders (0-6m: β=1.06 [-0.10, 2.23] mmol/mol/SD; *p*=0.074) or proposed mediators (β=0.63 [-0.52, 1.78] mmol/mol/SD; *p*=0.283) (Figure 3.4b; Table S8.7).

No evidence associating changes in 'carb/fat balance' or 'obesogenic' dietary patterns and HbA1c was found after adjustment for potential confounders and mediators during 6-12m and 0-12m periods (Figure S8.2; Table S8.7).

Figure 3.4: Associations between 1-SD increases in dietary pattern scores during 0-6 months and baseline-adjusted HbA1c at 6-months from multivariable linear regression.

a: Associations between a 1-SD increase in 'carb/fat balance' dietary pattern score and HbA1c change at 6 months; *b*: Associations between a 1-SD increase in 'obesogenic' dietary pattern score and HbA1c change at 6 months. *Model 1a* presents *Model 1* baseline-dietary pattern score adjusted associations in those with complete covariate data. *Model 2* presents associations adjusted for potential confounders: age, sex, baseline under-reporting status and change in total physical activity. *Model 3* presents model 2 associations adjusted for potential mediators: change in bodyweight and energy intake.



3.4.6 Sensitivity analyses

Multivariable linear regression analysis provided very strong evidence, regardless of level of adjustment, that reductions in bodyweight associated with the reductions seen in HbA1c (0-6m: β=-0.70 [95%CI: -0.95, -0.45] mmol/mol/kg lost; p<0.001) (Table S8.8). Additionally, there was strong evidence that both dietary patterns associated with weight change over 0-6m, with a 1-SD increase in 'carb/fat balance' dietary pattern score associating more strongly (β=-1.22 [-1.89, -0.55] kg/SD; p<0.001) than an equivalent 1-SD decrease in 'obesogenic' dietary pattern score (β=-0.77 [-1.31, -0.23] kg/SD; p=0.006) (Table S8.9). Within these models, there was strong evidence that baseline dietary pattern scores also associated with subsequent weight change over 0-6m, with baseline 'carb/fat balance' dietary pattern scores associating more strongly (β=-1.11 [-1.78, -0.45] kg per 1-SD higher pattern score; p=0.001) than baseline 'obesogenic' dietary pattern scores (β=-0.77 [-1.31, -0.23] kg per 1-SD lower pattern score; p=0.005). Higher baseline 'carb/fat balance' and lower baseline 'obesogenic' dietary pattern scores also associated with greater subsequent reductions in HbA1c within model 2 (β=-1.58 [-3.01, -0.14] mmol/mol/SD; p=0.031 and β=-1.18 [-2.33, -0.03] mmol/mol/SD; p=0.045 respectively) but not after further adjustment for bodyweight and TEI

change (β=-0.92 [-2.32, 0.49] mmol/mol/SD; *p*=0.199 and β=-0.69 [-1.80, 0.43] mmol/mol/SD; *p*=0.226 respectively).

No evidence was found for interaction between dietary pattern score and sex on HbA1c, or non-linear model trends (Figure S8.3 and Figure S8.4). During 0-6m, mechanism 1 and 2 effect sizes (β) remained largely unattenuated after restricting the sample to only those with complete covariate data (model 1-1a) and upon adjusting for potential confounders (model 1a-2) (Table S8.7).

3.5 Discussion

Our study examined whether nutrient-mediated dietary patterns are associated with glycaemic control independent of weight loss in people with type 2 diabetes for the first time. Weight loss was strongly associated with lowering HbA1c. We found evidence that increases in the 'carb/fat balance' dietary pattern score associated with reductions in HbA1c, independent of weight loss.

To our knowledge, this is the first study to use RRR to derive distinct dietary patterns theorised to relate to glycaemic control independently or via weight in patients with established type 2 diabetes. Increases in the 'carb/fat balance' dietary pattern associated with reductions in HbA1c regardless of initial diet quality or weight loss, in-keeping with our hypothesised nutrient pathway-related mechanisms. Effect sizes per 1-SD 'carb/fat balance' dietary pattern change were however small compared to the potential glycaemic benefits associated with weight loss. Weight loss therefore remains key for maximising glycaemic control in type 2 diabetes. The 'obesogenic' dietary pattern shared similar nutrient correlations and food group loadings with that seen in previous RRR investigations of obesogenic diets within the UK NDNS [325], indicating that the pattern derived within Early-ACTID was not sample-specific. Although associating with weight change as hypothesised, changes in 'obesogenic' dietary pattern scores did not associate with HbA1c change before or after adjusting for weight change. Examining the HbA1c association estimates in our study suggests if the 'obesogenic' dietary pattern is associated with HbA1c, it is a smaller association than for the 'carb/fat balance' pattern and our sample had insufficient power to confirm it.

Our study participants did not make large dietary pattern changes and were generally consuming what would be considered 'moderate' carbohydrate intakes at both 0- and 6-months, averaging 40-46% TEI. Average changes in 'carb/fat balance' dietary pattern scores did not, therefore, represent movement towards either 'high' or 'low' carbohydrate extremes [199]. Caution should therefore be exercised when extrapolating this study's findings outside of the domains of moderate carbohydrate

intakes. Those who increased their 'carb/fat balance' dietary pattern score were those who improved HbA1c to the greatest degree and were those found to be moving closer to UK healthy eating guidelines for total carbohydrate (50%TEI), fats (<35%TEI) and SFA (<11%TEI) [349–351]. Food group loadings for both dietary patterns we explored also revealed nutrient intake changes coincided with overall higher-quality food choices. Improvements in diet quality have been independently associated with greater cardiometabolic improvements, lower mortality and increased weight loss [352, 353]. Diets prioritising higher-quality food choices yet varying in macronutrient composition, such as Mediterranean-style and vegan diets, have also been associated with improvements in weight and glycaemic control in type 2 diabetes [302, 354]. Evidence from our study suggests that optimal dietary management of type 2 diabetes likely lies in both moderating combined carbohydrate and fat intakes and in maximising overall diet quality.

Our study has many strengths. Glucose-lowering medications were unchanged during 0-6m, meaning any changes in HbA1c could be attributed solely to lifestyle. Secondly, dietary intakes were assessed using 4-day food diaries, a measure less affected by dietary misreporting compared with other self-report methods [139, 140]. Third, diet measures were repeated at 3 separate timepoints, offering greater detail on effects of the dietary intervention at the primary (6-month) and secondary (12-month) timepoints. Fourth, RRR-derived dietary patterns isolated the best combinations of food intakes that explained intake differences in multiple nutrients hypothesised to relate to glycaemia or bodyweight. This contrasts with alternative methods like principal component analysis (PCA), which captures all variation in diet regardless of disease mechanisms. RRR also has an advantage over *a-priori* scores such as the Mediterranean diet index [295], which may not capture food intakes if such patterns are uncommon in a given population. Finally, analyses were adjusted with high-quality device-measured physical activity measured through accelerometry.

Limitations of this study include potentially biased model estimates due to differential missingness in sample data. Complete data during 0-6m was available in n=242 (41%) Early-ACTID participants. Compared with the whole sample (n=593), our sample were older, had lower baseline bodyweight and HbA1c, and saw greater reductions in bodyweight and HbA1c during 0-6m. Higher values of the HbA1c distribution were thus truncated, potentially downwardly biasing effect estimates. Secondly, the dietary pattern that explained maximal variation in carbohydrate and fat intakes associated with total amounts of these nutrients, regardless of quality (i.e. both sugar and fibre were higher), and was unable to capture differences in PUFA to as great a degree as other fats. We were thus unable to answer questions about whether patterns differentiating carbohydrate and fat quality associated with HbA1c change, as these were not the changes that participants made. Third, participants with

lower quality diets at baseline were found to be those who improved dietary pattern scores the most, and vice-versa, suggesting that extremes of dietary pattern score changes represent potential regression to the mean. However, we constructed models to include dietary pattern score at baseline so that change in our adjusted models represented a 1-SD increase in pattern score when people start from the same point. Fourth, we identified 56% of our sample as energy under-reporters, in line with under-reporting observed in adults in the UK NDNS [143]. This highlights a potentially high degree of error, however under-reporting was not associated with dietary pattern score and regression estimates were not attenuated by misreporting adjustment. Fifth, due to demographic characteristics in Early-ACTID participants, study results are mainly generalisable to a white population living in less socially deprived areas. Finally, although we adjusted for a number of potentially confounding variables, as with all observational analyses, residual confounding from unmeasured confounders cannot be ruled out.

3.6 Conclusions

In newly diagnosed people with type 2 diabetes, promoting weight loss should remain the primary nutritional strategy for improving glycaemic control. However, improvements in dietary pattern quality that bring carbohydrate and fat intakes more in line with general healthy eating targets may provide small, additional improvements in HbA1c.

3.7 Ethics approval and consent to participate

Early-ACTID was approved by the Bath Research Ethics Committee (05/Q2001/5), and all participants provided written informed consent.

3.8 Availability of data and materials

Data supporting the findings of this study are not openly available due to consent not being sought at the time of the trial. However, authenticated researchers may apply for access to the data via the University of Bristol data.bris research repository (DOI: 10.5523/bris.3o7bip8v2ae8m2gdfpu1pt5rlz).

3.9 Implications for thesis

Findings from study 1 indicate that achieving weight loss is the predominant factor linked with improving glycaemic control, in line with the current evidence base. However, regardless of weight change, changing dietary patterns by improving overall food quality and balancing total carbohydrate and fat intakes around general healthy eating recommendations could provide additional, albeit small, benefits to glycaemia. Findings from study 1 thus provide evidence that a 'carb/fat balance' dietary pattern associates with glycaemia directly, potentially being a candidate pattern for detecting associations between diet and longer-term glycaemic deterioration in early T2DM, if they exist. This will be explored further in studies 3 and 4 of this thesis (Chapter 5 and Chapter 6 respectively). However, changes in dietary patterns were not maintained across the full 12-months of the Early-ACTID trial. Average pattern scores improved during the first six months of the trial but reverted back towards baseline during the second six months. Long-term dietary pattern trajectories following the Early-ACTID dietary intervention were thus deemed appropriate for specific exploration within study 2, allowing assessment of whether the typically divergent dietary behaviours exhibited by men and women perhaps contributed to intervention response.

Chapter 4 - Study 2: Do men and women's dietary pattern change diverge after a non-prescriptive dietary intervention?

4.1 Introduction

Data presented in Chapter 3 indicated that data-driven dietary patterns in Early-ACTID during 0-6 months became less 'obesogenic' overall; intakes became lower in energy-density and fat and higher in fibre, but were not explored further by sex. Exploring for sex-differences in dietary pattern change could inform on whether patient-centred dietary interventions in type 2 diabetes (T2DM) require additional tailoring by sex or gender to improve short- or long-term dietary patterns similarly in both men and women.

Dietary patterns are typically found to differ between men and women [31, 32, 325], relating to differences in both biology and gender behavioural norms [33, 34]. In the UK, men report following dietary patterns higher in meats, sugary foods, fried foods and refined grains and lower in fruits and vegetables compared to women [31]. Although neither sex are observed to adhere strongly to healthy eating guidelines [355], men typically report following diets lower in healthy foods and higher in unhealthy foods [32]. However, the evidence for typical dietary patterns in men and women with T2DM remains scant as dietary intakes are typically reported combined. One study reporting differences in specific food intakes by sex was an Italian cross-sectional study of 2,573 people with T2DM (60% men; mean age 62 years, disease duration 8.5 years and BMI 30.3 kg/m^2) by Vitale et al [356]. Women reported consuming more legumes, fruits, vegetables, olive oil, eggs, milk and added sugars, whereas men reported consuming more starchy foods (pasta and bread), soft drinks and alcohol using a 281-item FFQ. A separate 21-item FFQ assessment of food group intakes in 1,516 Japanese men and women with T2DM at baseline of the Japanese Diabetes Complications (cohort) Study (53% men; mean age 58 years, disease duration 11 years and BMI 22.9 kg/m^2) [357], indicated women consumed slightly greater amounts of fruits and vegetables whilst men consumed considerably more alcohol. However, due to the gastronomic background of Italy potentially facilitating more of a Mediterranean-style dietary pattern, and the generally unique food culture that exists in Japan, it is difficult to infer how intakes compare in men and women with T2DM within the UK. How differing food attitudes and behaviours impact on the eating habits and dietary patterns of men and women with T2DM, and in turn, how they might affect dietary responses

following dietetic advice, remains largely unexplored. To maximise dietary pattern change for both men and women, a dimorphic approach may be required.

Although differences in biology may play some role [33], common differences in dietary intakes between men and women can be explained predominantly through differences in gender social norms; of which there are many [34]. Data collected from population-based surveys indicates that women in Western societies consistently report being more aware of the health impacts of their dietary choices compared with men, who have typically reported prioritising taste and convenience over health [34, 358–361]. In older age groups, the purchasing, preparing and provision of food has historically been a role performed by women rather than men [362], potentially impacting diet quality in men who report lacking sufficient knowledge and skills, especially when living alone [363, 364]. Higher levels of dietary restraint, evident more commonly in women [34, 365], is associated with reduced energy-intakes and diets with reduced energy density [366, 367]. A substantial body of literature clearly indicates women are more likely to make dietary choices based on concerns regarding bodyweight and body-image compared with men [368–371], although gender differences in bodyweight attitudes have been observed to disappear as BMI increases above 35kg/m^2 [371]. Neuroimaging studies have also indicated that women typically respond to hedonic eating behaviours with greater cognitive conflict and guilt compared with men [33], reacting more strongly to images of hedonic foods but without necessarily leading to increased energy intakes [372]. However, such studies have typically involved only small numbers (n~20) of young (mean ages 21-35 years) men and women with healthy BMI and without comorbidities [33, 372]. Brain function in relation to food reactivity in older men and women has so far not been investigated. In response to stress however, women have been observed to make more impulsive and reward-oriented food choices compared with men [33, 34], consuming more sweet snack foods like chocolate, confectionary and ice-cream [373]. Although sex-differences in food response during stress appears to be a consistent finding [34], data on 'comfort-eating' behaviours were obtained from self-report through mail and online surveys only, and again involved mainly young, healthy adults. It is unclear therefore whether such food responses apply to men and women living with T2DM. For example, a cross-sectional study in 540 Italian adults (58% men) with T2DM observed that women reported higher levels of self-care maintenance, health monitoring, and disease management compared with men [374]; in potential opposition to stress responses in younger, healthier individuals.

Given differences appear to exist in typical attitudes and eating behaviours between men and women, it is possible such differences impact the dietary response to lifestyle intervention in people with T2DM. As introduced in section 3.3.2, the Early-ACTID trial [326] used a non-prescriptive,

patient-centred dietary intervention aiming to achieve 5-10% weight loss in people newly-diagnosed with T2DM. Patient-centred care is defined as "*providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions*" [375], and is considered best practice within modern healthcare and dietetics [30, 63]. Thus, although dietary advice included choosing foods lower in energy-density and fat and higher in fibre to aid weight loss [376, 377], specific dietary changes were chosen by trial participants in line with their personal preferences and values. The aforementioned behavioural differences relating to sex and/or gender will potentially affect the short- and long-term dietary pattern changes seen under this non-prescriptive approach.

Previous analysis of short-term (0-6 month) food and nutrient changes made by participants of the Early-ACTID trial did find certain differences made between men and women [376]. Men (n=175) reported reductions in absolute intakes of alcohol, sweet and savoury treat foods, nuts, cheese and lower-fibre breakfast cereals, whilst women (n=87) reported reductions in curries, casseroles, ready meals, rice and pasta, alongside increases in high-fibre breakfast cereals. Differences in the degree of change in food group intakes between men and women during 0-6 months were not formally assessed and it is unclear how combined dietary intakes changed separately in men and women during the intervention. Men reported greater reductions in absolute energy intakes compared with women (mean (SD): -218 (332) vs -123 (270) kcal/day), although energy changes as a proportion of requirements were not assessed and weight loss was found to be the same in both sexes at 6 months [377]. Dietary change in men and women after the first 6 months of the Early-ACTID intervention have not been investigated.

The following study therefore explores whether differences exist between men and women in dietary pattern change during and after a 12-month, non-prescriptive, patient-centred dietary intervention in early T2DM. It again uses a data-driven dietary pattern analysis to inform on what changes occur in men and women in multiple nutrient and food intakes simultaneously, during both the Early-ACTID intervention itself (0-12 months) and its subsequent follow-up (1-6 years). The aim is to inform on whether typical non-prescriptive, patient-centred dietary advice requires tailoring further by sex for achieving similar dietary pattern changes in both men and women.

4.2 Methods

4.2.1 Sample

Data came from participants who took part in the Early-ACTID trial [326] and its post-intervention follow-up. The Early-ACTID trial and intervention is described in detail in sections 3.3.1 and 3.3.2. Briefly, the study was a 12-month, multi-centre, parallel-group randomised controlled trial (RCT) involving 593 adults diagnosed in the previous 5-8 months with T2DM. Participants were randomised to either a usual care, dietary intervention or diet with physical activity intervention group. Dietary advice given to both of the intervention groups was provided through goal-oriented motivational interviewing [378] and was non-prescriptive, based around nutritional guidelines at the time of the trial. Following the end of the trial, consenting participants (N=476) were invited to annual consultations for usual care and monitoring by trial clinicians for a further five-years. Only those participants who had received the diet or diet with physical activity intervention during the trial were included in the current analysis.

4.2.2 'Obesogenic' dietary pattern derivation

Data on energy-dense, higher-fat, lower-fibre 'obesogenic' dietary patterns derived via reduced-rank regression (RRR) from 4-day food diary data at baseline were used to generate equivalent dietary pattern scores at follow-up timepoints (6 months, 12 months, 3 years and 6 years) using the methods described in sections 3.3.3 and 3.3.4. As stated in section 3.4.3, higher 'obesogenic' dietary pattern scores associate with greater consumption of low-fibre bread, processed meat, coated chicken/fish, fried/roast potatoes/chips and biscuits/cakes, and lower consumption of fresh fruit, raw/boiled/grilled vegetables, yoghurts, boiled/baked potatoes and meat substitutes.

4.2.3 Misreporting of energy intake

In line with the methods for assessing misreporting at baseline described in section 3.3.5, dietary misreporting at 3 years and 6 years was assessed via an individualised method [143] comparing reported energy intake to estimated energy requirements. As few over-reporters were identified at baseline (n=4), 3 years (n=2) and 6 years (n=3), these were combined with plausible-reporters and a binary categorical variable (under-reporter and plausible-reporter) was created for analyses. An

intraclass correlation coefficient (ICC) for under-reporting status change over time was calculated using a random intercept logistic multilevel model with under-reporting status as outcome and with no predictors. The calculated ICC was 0.98, suggested only 2% under-reporting status variation over time occurred within-persons. Under-reporting status was therefore considered to remain stable within-individuals over time and only a baseline under-reporting status variable was used within analyses.

4.2.4 Other measures and covariates

Diet, physical activity, anthropometry, medications and clinical measures were assessed at five timepoints (0-, 6-, 12-months, 3- and 6-years post-randomisation). Baseline physical activity was assessed over 7 days via waist-worn, uni-axial accelerometers (Actigraph GT1M; Actigraph LLC, Pensacola, FL, USA), with data processing as detailed previously [347]. Participants were scored against the 2007 UK Index of Multiple Deprivation (IMD) based on their home postcode at baseline [379]. Glucose-lowering medications, namely metformin, sulphonylureas, glitazones, alpha-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 agonists and insulin were recorded by trial clinicians as type and dose. To maximise the statistical power of the analysis given low participant numbers taking non-metformin and sulphonylurea medications (Table S8.11), glucose-lowering medications were combined into two separate variables. These variables were sums of percentage of maximum doses of 1) 'appetite-affective' medications (metformin, GLP1 agonists, alpha-glucosidase inhibitors and DPP4 inhibitors) and 2) 'hypo-affective' medications (sulphonylurea and insulin; where taking any insulin was classed as 100% maximum dose). 'Appetite-affective' and 'hypo-affective' medication variables were named based on the potential impact of these medications to reduce appetite or induce hypoglycaemic episodes respectively [380], and in turn, the potential to affect dietary intakes reactively. As sex is assigned at birth and predates common correlates of diet, associations between sex and dietary patterns were considered free of distortion by confounding variables. However, baseline under-reporting status, time-varying 'appetite-affective' and 'hypo-affective' medications and trial intervention group were explored as potential suppression mediators within post-hoc analyses (see section 4.2.6).

4.2.5 Statistical analysis

Variables were described using the mean (SD) if approximately symmetrical or median (quartile 1, quartile 3) otherwise. Random intercept multilevel models (Information S8.4) with repeated measurements (level 1) nested within participants (level 2) were used to examine trajectories over time for 'obesogenic' dietary pattern scores (Model 1). Multilevel models estimate mean trajectories of a specified outcome over time and account for the intra-person dependency of measurements over time. A balanced dataset is not required meaning individuals who contributed fewer than the maximum number of observations are retained within analyses under a Missing At Random (MAR) assumption [381] (Information S8.5). As the primary and secondary endpoints of the Early-ACTID trial were at 6 and 12 months respectively [326], with medications being held constant during 0-6 months only, diet trajectories were modelled using a linear spline for periods 0-6m, 6-12 months (6-12m) and 1-6 years (1-6y). Measurement times were modelled as continuous to account for measurement time variation during each measurement wave, with spline breakpoints after 6-months and 12-months set to median measurement values; 0.58 years (6.9 months) and 1.07 years (12.8 months) respectively (Table S8.12). Predictors in Models 1 were time-period, sex and an interaction term between sex and time-period, producing one model estimate for male versus female differences in dietary pattern change per period. All models were run using maximum-likelihood estimation. To assess validity of results from Model 1, graphical diagnostics were performed to assess assumptions of residual normality and homoscedasticity (over time and over predicted values for dietary pattern scores).

Both trial intervention groups received the same dietary intervention. Even though the diet with physical activity group received additional advice on increasing physical activity, both intervention groups saw equivalent trial outcomes [326]. Therefore, intervention groups were combined and modelled as a single cohort. Units of dietary pattern change effect estimates within Model 1 were for a 1-SD change in baseline dietary pattern score over a 6-month period; estimates for periods 0-6m and 6-12m periods can thus be considered to reflect total change during these periods. Evidence of association was considered when $p<0.05$ for each interaction term between sex and time-period. The strength of evidence was also assessed by interpreting the clinical relevance of their β and 95%CI. To assess overall change in 'obesogenic' dietary pattern scores in the whole sample during each period, Model 1 was also repeated without adjustment for sex (Model 0).

4.2.6 Post-hoc statistical analysis

After Model 1 was performed, post-hoc analyses were performed to explore whether differences in dietary pattern change between sexes were being masked by inconsistent mediation [382] (Information S8.6). Model 1 was therefore adjusted for potential suppression mediators: 1) baseline under-reporting status (Model 1a) and 2) time-varying glucose-lowering medications (Model 1b). For the latter analysis, 'appetite-affective' and 'hypo-affective' medication dose variables were disaggregated into their between-person and within-person components [381]. Specifically, variables were split into a time-invariant person-mean medication dose (i.e. average dose across all timepoints) variable and a timepoint-specific deviation from the person-mean medication dose (i.e. the difference between person-mean dose and the dose taken at a particular timepoint) variable. Model 1 was then adjusted for these disaggregated variables and for their interactions with each time-period in Model 1b. Evidence of inconsistent mediation would be considered if associations between sex and dietary pattern change became stronger following adjustment.

An additional set of post-hoc analyses were performed to explore sex differences in changes of single nutrient factors relating to the construction of the 'obesogenic' dietary pattern. Specifically, random intercept linear spline multilevel models were run as described in section 4.2.5 but with the following dietary variables as outcomes: total energy intake (Model 2a), percentage energy intake relative to baseline (Model 2b; restricted to sample with available baseline dietary data), food energy-density (Model 3), percentage energy from fat (Model 4) and fibre-density (Model 5). To assess validity of results from Models 2-5, graphical diagnostics were performed to assess assumptions of residual normality and homoscedasticity (over time and over predicted outcome values).

4.2.7 Missing data analysis

To assess whether Model 1 estimates were biased by missing dietary data across different time-periods, two binary dietary data missingness pattern indicators were created and assessed for associations with sex (exposure) and dietary pattern scores at each timepoint (outcome) using simple logistic regression. Missingness pattern indicator 1 represented missing dietary data patterns relating to study attrition from the 12-month or 3-year timepoint (left study=1, remained in study=0). Missingness pattern indicator 2 represented all other missingness patterns of dietary data not explained by indicator 1. To estimate potential selection bias, differences in sample

characteristics were compared descriptively between those in our analysis sample and all those who received an intervention.

4.2.8 Sensitivity Analyses

To confirm that the addition of physical activity advice was not affecting main model estimates, Model 1 was adjusted for trial arm (Model 1c). To confirm whether the 'obesogenic' dietary pattern structure (i.e. the size or direction of food group loadings for pattern scores) changed over time, RRR was repeated independently at 3- and 6-years and compared the first patterns derived at these timepoints with the first patterns at baseline using Tucker's congruence coefficient (CC) [342] (comparisons between baseline and 6- and 12-month patterns were conducted within Study 1; see section 3.3.4). This was also repeated across timepoints but restricted to only those participants with data available at 3-years for exploring potential effects relating to sample size. A CC>0.85 was taken to indicate dietary patterns were structurally similar between timepoints [342]. Similarly, to confirm that the 'obesogenic' dietary pattern was structurally stable between sexes, we assessed dietary pattern congruence at baseline in men and women after running RRR in each sex separately.

Analyses were performed in Stata (v15; StataCorp LLC, College Station, TX, USA), with the RRR procedure incorporating SAS (v9; SAS Institute, North Carolina, USA) (Information S8.3).

4.3 Results

4.3.1 Sample characteristics

Dietary data for one or more timepoints were available in N=331 participants (67% of those enrolled at baseline), of which n=214 (65%) were male and n=117 (35%) were female (Figure 4.1). At each specific timepoint, dietary data were available for n=285 (66% male), n=266 (66% male), n=268 (66% male), n=127 (70% male) and n=178 (69% male) participants at 0-, 6-, 12-months, 3- and 6-years respectively. Equal numbers of male participants came from each intervention group (50% per group) and slightly more females had received the diet only intervention (54%) versus the diet with physical activity intervention (46%) (Figure 4.1). Compared to all intervention participants, participants in the analysis sample at baseline were slightly older (median 62 vs 61 years), had

slightly lower bodyweight and BMI (87.0 vs 88.7 kg; 29.6 vs 30.1 kg/m^2) and lost slightly more weight during 0-6m (-2.0 vs -1.7 kg) but were otherwise similar (Table S8.13). Neither sex nor dietary pattern scores were found to associate with missingness patterns in the diet data (Table S8.14 and Table S8.15), indicating missing dietary data could be assumed to be MAR.

Comparing men and women in our analysis sample at baseline (Table 4.1), women were slightly younger than men (median 61 vs 63 years), less physically active (249 vs 296 total activity counts per minute; 16 vs 24 minutes of moderate-to-vigorous physical activity (MVPA) per day), lived in slightly more deprived areas (14 vs 12 IMD score), had lower weight but higher BMI (81.8 vs 89.6 kg; 30.8 vs 29.4 kg/m^2) and were classified as less likely to under-report energy intake (62% vs 51%). Women also took more glucose-lowering medications at baseline compared to men (39% vs 33% 'appetite-affective' and 9% vs 8% 'hypo-affective' medications), but this trend reversed by 6 years, with fewer women taking glucose lowering medications than men (49% vs 54% 'appetite-affective' medications and 17% vs 22% 'hypo-affective' medications). Raw mean bodyweight trajectories in each sex over time are displayed in Figure 4.2. Both men and women lost small amounts of weight during 0-6m (mean weight loss 2.8kg and 3.5kg in men and women respectively) but mean weight gradually increased in both sexes over the remainder of the study. Bodyweight however remained slightly lower at 6 years compared to at baseline in both sexes (80.8 vs 81.8 kg in women and 87.3 vs 89.6 kg in men).

Figure 4.1: Sample size flow chart.

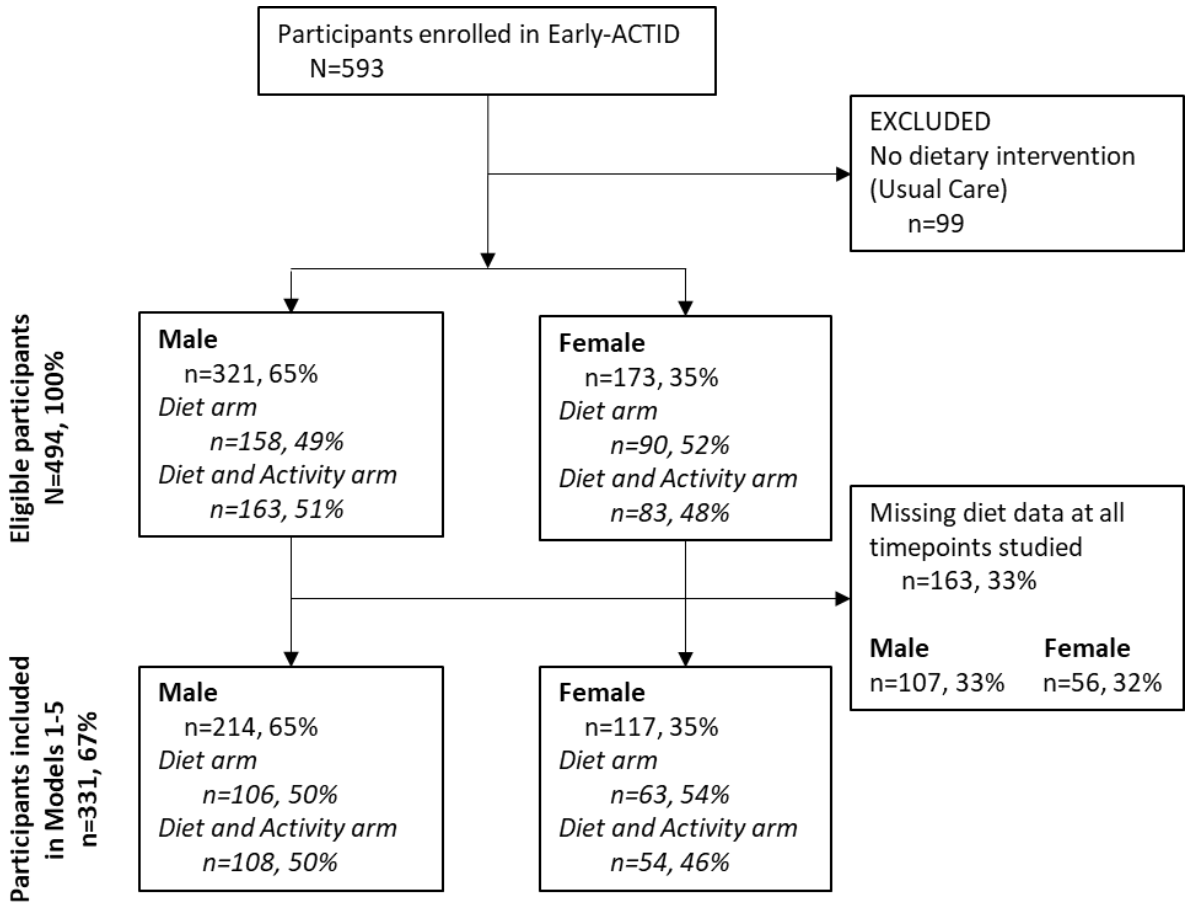


Table 4.1: Comparison of baseline characteristics of males and females included within Models 1-5.

	Male	Female
N (%)	214 (65%)	117 (35%)
Age (years)	63 (56, 69)	61 (54, 67)
Total physical activity (cpm)	296 (239, 373)	249 (198, 321)
MVPA (mins)	24 (14, 37)	16 (7, 27)
IMD score	12.3 (6.9, 18.6)	14.3 (8.0, 20.6)
Weight (kg)	89.6 (81.4, 97.0)	81.8 (71.2, 92.6)
BMI (kg/m^2)	29.4 (27.3, 31.9)	30.8 (27.3, 35.6)
Under-reporting status[a] (n(%))	117 (62%)	49 (51%)
On 'appetite-affective' medications (n(%))	70 (33%)	46 (39%)
'Appetite-affective' medications (%max dose)	0 (0, 33)	0 (0, 33)
On 'hypo-affective' medications (n(%))	18 (8%)	11 (9%)
'Hypo-affective' medications (%max dose)	0 (0, 0)	0 (0, 0)

Data presented as n(%) or median (quartile 1, quartile 3). [a] Under-reporting status is available for those with baseline dietary data only (n=285). *cpm – counts per minute; MVPA - moderate-to-vigorous physical activity; IMD – index of multiple deprivation; BMI – body mass index.*

Figure 4.2: Raw mean (95%CI) bodyweight trajectories in males (N=214) and females (N=117). Values are displayed at median measurement times for each individual timepoint.

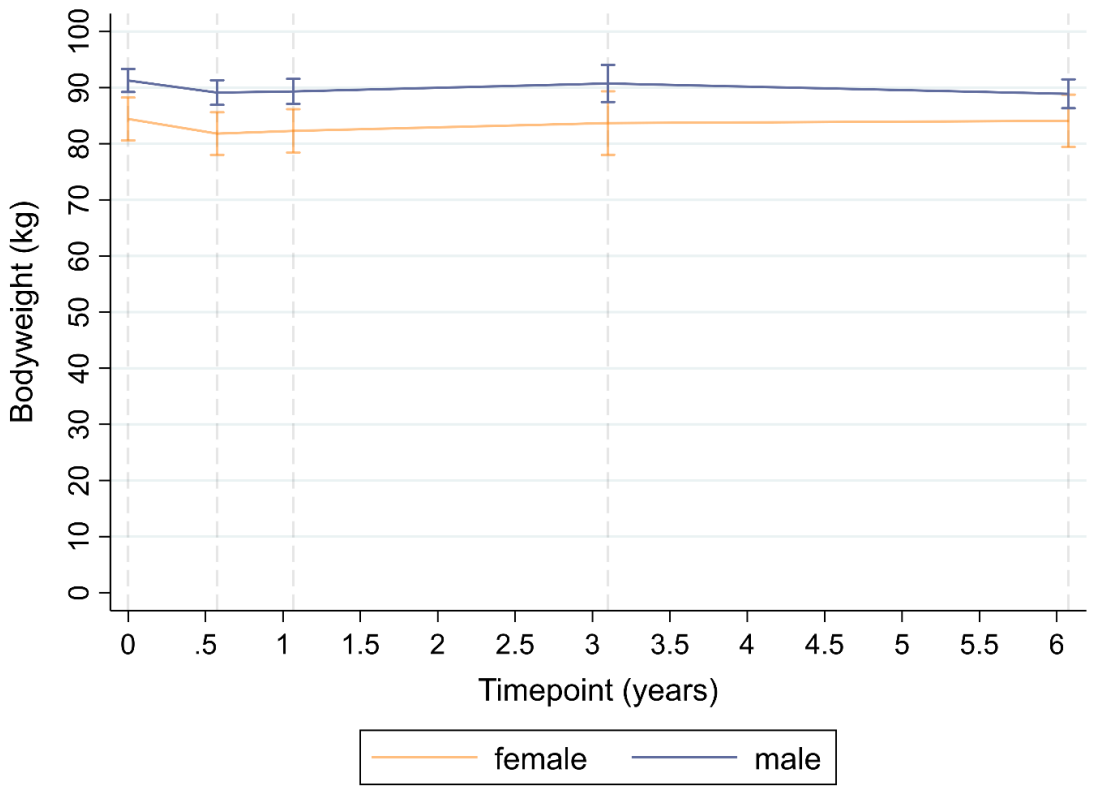


Table 4.2: Modelled baseline values in males and females for 'obesogenic' dietary pattern scores (Model 1) and secondary dietary outcomes (post-hoc Models 2a-5).

Baseline values of energy intake as percentage of baseline derived from Model 2b are not presented due to being constrained to 100% in both sexes.

			Male		Female		Difference (Female – Male)		
Model	**N**	**Dietary component**	**β**	**95%CI**	**β**	**95%CI**	**β**	**95%CI**	**p_{diff}**
1	331	Baseline dietary pattern score (SD)	0.09	-0.05, 0.23	-0.22	-0.42, -0.03	-0.32	-0.56, -0.08	**0.010**
2a	331	Baseline energy intake (kJ)	7890	7648, 8131	6652	6319, 6985	-1238	-1649, -826	**<0.001**
3	331	Baseline energy-density (kJ/g)	6.6	6.4, 6.8	6.2	5.9, 6.4	-0.4	-0.7, -0.1	**0.006**
4	331	Baseline fat intake (%TE)	33.9	33.1, 34.7	33.6	32.4, 34.7	0.3	-1.1, 1.8	0.651
5	331	Baseline fibre-density (g/MJ)	2.2	2.1, 2.3	2.4	2.3, 2.6	0.3	0.1, 0.4	**0.001**

4.3.2 Obesogenic dietary patterns at baseline

Baseline differences between male and female dietary intakes in Models 1-5 are shown in Table 4.2. Men had more 'obesogenic' dietary patterns at baseline compared to women, with intakes higher in total energy and energy-density and lower in fibre-density. There were no differences between men and women in fat intakes as a percentage of total energy at baseline (Table 4.2). At baseline, men reported having higher median alcohol intakes compared to women (5% vs 0% TEI) and lower median combined starches and sugar intakes (43% vs 45% TEI).

4.3.3 Obesogenic dietary pattern changes following a non-prescriptive dietary intervention

Boxplots of raw dietary change for men and women in each period are shown in Figure 4.3. In Model 0 for men and women combined, 'obesogenic' dietary pattern scores decreased by β=-0.23 [95%CI: -0.34, -0.11] SD/6-months (p<0.001) during 0-6m, remained similar during 6-12m (β=0.10 [-0.04, 0.24] SD/6-months; p=0.152), increasing at a slow rate over 1-6y (β=0.02 [0.01, 0.03] SD/6-months; p=0.008). However, there was no evidence of sex-differences in dietary change during any period for 'obesogenic' dietary pattern scores in Model 1, nor for energy-density, percentage energy from fat or fibre-density in post-hoc Models 3-5 (Table 4.3). Total energy intakes in both sexes reduced during 0-6m and 6-12m and remained lower relative to baseline throughout 1-6y (Table 4.3). Women reduced raw energy intakes to a lesser degree than men during 0-6m (β_{diff}=385 [42, 727] kJ/6m; p=0.028; N=331), but there was no evidence for sex differences when assessing change as a percentage of baseline intakes (β_{diff}=4.3 [-0.1, 8.7] %; p=0.057; sample restricted by available baseline data, N=285) (Table 4.3). There was no evidence for sex differences in either change in raw energy intake or in change as a percentage of baseline intake during 6-12m or 1-6y periods. Model diagnostics revealed no major issues with residual normality or homoscedasticity (Figure S8.5 to Figure S8.11).

Post-hoc analyses revealed no evidence of suppression mediation of associations between sex and dietary pattern trajectories by misreporting status or glucose-lowering medication intake (Table S8.16).

Figure 4.3: Box-plots of raw dietary changes in males and females for each study period.

a – 'obesogenic' dietary pattern score change; b - total energy intake change; c - total energy intake as percentage of baseline change; d - dietary energy-density change; e – fat intake change as a percentage of total energy intake; f – fibre-density change.

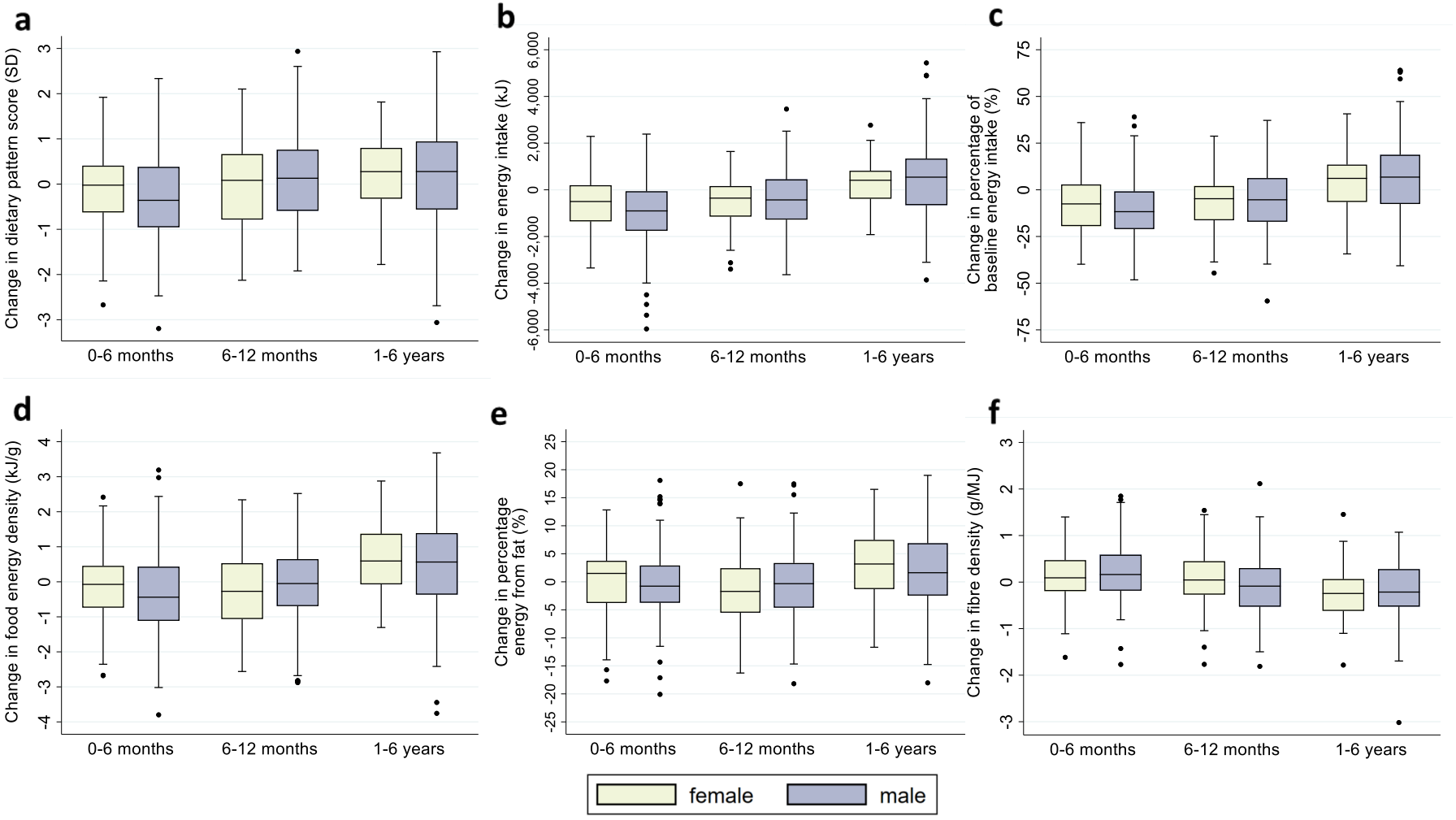


Table 4.3: Modelled changes in diet for each period of study within and between sexes.

β's and 95%CI represent change in dietary component intakes per 6-month period; changes presented for 0-6m and 6-12m can therefore be considered to represent total change during these periods.

			Male		Female		Difference (Female – Male)		
Model	**N**	**Dietary component**	**β**	**95%CI**	**β**	**95%CI**	**β**	**95%CI**	**p_{diff}**
1	331	Dietary pattern change 0-6m (SD/6-months)	-0.26	-0.40, -0.12	-0.16	-0.35, 0.04	0.10	-0.13, 0.34	0.393
		Dietary pattern change 6-12m (SD/6-months)	0.18	0.01, 0.35	-0.06	-0.30, 0.18	-0.24	-0.53, 0.06	0.114
		Dietary pattern change 1-6y (SD/6-months)	0.01	0.00, 0.03	0.03	0.01, 0.06	0.02	-0.01, 0.05	0.183
2a	331	Energy change 0-6m (kJ/6-months)	-813	-1014, -613	-428	-706, -151	385	42, 727	**0.028**
		Energy change 6-12m (kJ/6-months)	-238	-483, 7	-438	-786, -91	-200	-625, 224	0.355
		Energy change 1-6y (kJ/6-months)	40	15, 66	21	-17, 60	-19	-65, 27	0.418
2b	285	Percentage energy change 0-6m (%/6-months)	-9.5	-12.1, -6.9	-5.2	-8.8, -1.6	4.3	-0.1, 8.7	0.057
		Percentage energy change 6-12m (%/6-months)	-2.8	-6.0, 0.4	-6.1	-10.6, -1.5	-3.3	-8.9, 2.3	0.248
		Percentage energy change 1-6y (%/6-months)	0.6	0.3, 1.0	0.2	-0.3, 0.7	-0.4	-1.0, 0.2	0.195
3	331	Energy density change 0-6m (kJ/g/6-months)	-0.3	-0.5, -0.2	-0.2	-0.4, 0.1	0.1	-0.1, 0.4	0.308
		Energy density change 6-12m (kJ/g/6-months)	0.1	-0.1, 0.3	-0.2	-0.5, 0.1	-0.3	-0.6, 0.1	0.113
		Energy density change 1-6y (kJ/g/6-months)	0.0	0.0, 0.1	0.1	0.0, 0.1	0.0	0.0, 0.1	0.465
4	331	Fat intake change 0-6m (%TE/6-months)	-0.3	-1.2, 0.6	0.2	-1.0, 1.4	0.5	-1.1, 2.0	0.559
		Fat intake change 6-12m (%TE/6-months)	-0.4	-1.5, 0.7	-1.7	-3.2, -0.2	-1.3	-3.2, 0.6	0.173
		Fat intake change 1-6y (%TE/6-months)	0.2	0.1, 0.3	0.3	0.1, 0.4	0.1	-0.1, 0.3	0.496
5	331	Fibre density change 0-6m (g/MJ/6-months)	0.2	0.1, 0.3	0.1	-0.0, 0.2	-0.1	-0.3, 0.0	0.141
		Fibre density change 6-12m (g/MJ/6-months)	-0.1	-0.3, 0.0	0.0	-0.2, 0.2	0.1	0.0, 0.3	0.137
		Fibre density change 1-6y (g/MJ/6-months)	0.0	0.0, 0.0	0.0	0.0, 0.0	0.0	0.0, 0.0	0.436

4.3.4 Sensitivity analyses

There was no evidence that receiving the diet only or diet with physical activity intervention affected differences in dietary pattern trajectories between men and women (Table S8.16). Running RRR at each timepoint independently demonstrated that dietary patterns were structurally similar at baseline and 6-years (CC>0.85), but differed at 3-years (CC=0.81) (Table S8.17 and Figure S8.12). The highest positive and negative loading food groups differed in the 3-year dietary pattern compared to at baseline, with 'eggs and egg dishes' (Baseline vs 3-years: 61% vs 61% consumers; median intake (Q1, Q3): 14 (0, 29) vs 14 (0, 30) g/day) and 'high fat milk and cream' (26% vs 19% consumers; 0 (0, 0) vs 0 (0, 3) g/day) loading more prominently to increase pattern scores at 3-years, and 'raw/boiled/grilled vegetables' (99% vs 99% consumers; 116 (85, 167) vs 137 (76, 189) g/day) and 'boiled/baked potatoes' (79% vs 89% consumers; 50 (28, 90) vs 58 (30, 90) g/day) loading more prominently to decrease pattern scores at 3 years. Additionally, 'coated chicken and fish' (21% vs 23% consumers; 0 (0, 0) vs 0 (0, 0) g/day) and 'crisps and savoury snacks' (27% vs 18% consumers; 0 (0, 3) vs 0 (0, 0) g/day) loaded less prominently on pattern scores at 3 years compared to at baseline. Explained nutrient and food intake variation and pattern score correlations with RRR nutrient intermediate intakes were however the same across timepoints (Table S8.18). Repeating RRR at each timepoint independently in only those participants with dietary data available at 3 years (N=127) changed congruence of dietary patterns between baseline and 12-months and 6-years from 'fair' (CC=0.90) to 'poor' (CC<0.85) (Table S8.19), suggesting poor pattern congruence between baseline and 3-years was a result of the reduced sample size at 3-years. The 'obesogenic' dietary pattern was found to be structurally stable between men and women (CC=0.85; Table S8.20) following running RRR in each sex separately at baseline.

4.4 Discussion

In this study, sex-differences were assessed in dietary change following a non-prescriptive, patient-centred dietary intervention in early T2DM. Dietary pattern changes made by both sexes were small and were not maintained over the long-term. Despite differences in intakes at baseline there were no sex-differences in how dietary patterns, relative energy intakes or nutrient intakes changed either during the intervention (0-12 months) or during follow-up (1-6 years).

Men and women were observed to respond equally to non-prescriptive, patient-centred dietary advice typical of the approach used in current UK dietetic practice. No evidence was found to

indicate such interventions be tailored further by sex for achieving similar dietary pattern change in both men and women. A patient-centred approach tailors advice to the individual and potentially negates the behavioural trait differences that have been found to exist between men and women [34]. Only raw energy intakes were seen to reduce during 0-6m to a greater degree in men compared with women; attributed previously to greater reductions in alcohol intake in men within Early-ACTID [377]. No sex-differences in absolute energy intakes were observed during other periods. Men have higher energy requirements compared to women due to greater lean body mass. Absolute energy intake reductions might therefore be expected to be greater in males despite relative energy intake reductions being equal between sexes. In line with this, there was no evidence for sex-differences in percentage energy intake change during 0-6m, suggesting relative energy intake changes were indeed the same in both sexes. Complete baseline data was however required in the latter model, leading to a reduced sample size for analysis (N=285 vs 331) and hence power for detecting potential associations. However, weight change may serve as a suitable proxy measure of true rather than reported energy intake change [383], and no evidence was found for weight-loss differing by sex in the Early-ACTID trial [377]. In the first 12-months of the Look AHEAD trial; currently the largest RCT involving patients with T2DM (n=5145; 59% female), men were found to lose a greater percentage of initial weight compared with women (mean -9.2% vs -8.1%) [384, 385]. The Look AHEAD intervention was however prescriptive and consisted of low-fat dietary advice but also periods of low-calorie meal replacement drinks at varying frequency, therefore differing from Early-ACTID's non-prescriptive approach. Additionally, differences in weight loss between men and women were not observed longer-term within Look AHEAD [386] and it is unclear whether prescribed calorie deficits were tailored by sex, potentially contributing to the greater initial weight loss seen in men versus women. Additionally, a systematic review by Robertson et al [387] of 22 weight-loss RCTs lasting over 12 months, which included results of the Look AHEAD trial but was not restricted to people with T2DM, found no conclusive evidence that weight-loss differences exist between men and women following the same intervention. Maintaining long-term adherence to dietary change is also a recognised difficulty following nutritional interventions [208, 388], with weight regain after initial weight-loss common [389, 390]. A systematic review by Varkevisser et al [391] of 42 RCTs and 7 observational studies investigating determinants of weight maintenance following weight loss, similarly found no evidence of differences between men and women. The reviews by Robertson et al [387] and Varkevisser et al [391] were not specific to people with T2DM who typically have greater metabolic dysfunction, differentially affecting each sex to varying degrees [126]. Interventions in both systematic reviews also varied in the type of diet, exercise and/or behavioural change techniques used and trials inconsistently reported levels of intervention

adherence, energy intake, or physical activity levels. Also, most participants within the reviews were female (64-72%), highlighting a historical fact that males are typically under-represented in weight-loss interventions [387, 392]. Given these limitations, more sex-specific research is needed to answer whether men and women with T2DM respond differently during weight loss interventions. However, the lack of evidence for sex-differences in weight loss within Early-ACTID [377], as well as the lack of conclusive findings within the current literature [387, 391], suggest sex-differences in relative energy intake change following lifestyle intervention are likely to be absent or small and clinically inconsequential.

Although dietary pattern changes were similar over time in both men and women in Early-ACTID, men had consistently more 'obesogenic' dietary patterns across the 6 years of the study. This agrees with men having higher 'obesogenic' dietary pattern scores more generally within the UK, based on analysis of data from the UK National Diet and Nutrition Survey (NDNS) [325], as well as reporting lower quality eating patterns compared to women more globally [32, 34, 356]. However, mean 'obesogenic' dietary pattern scores in men and women differed by only 0.32 SD in participants of Early-ACTID. Results from Study 1 of this thesis indicate that an 'obesogenic' dietary pattern score difference of 0.32 SD is associated with negligible differences in weight (0.2 kg) and with no evidence of association with HbA1c (see sections 3.4.5 and 3.4.6). In Vitale et al's study of 2,573 Italian people with T2DM highlighted within the introduction (section 4.1); one of the few existing studies that detail food intakes separately for men and women with T2DM, women reported consuming more high quality foods in general compared with men [356]. However, women were also scored overall slightly worse for adherence to European Association for the Study of Diabetes (EASD) low-fat, nutrient-based dietary guidelines [356, 393], potentially as a result of men's four-fold higher intake of alcohol affecting relative macronutrient contributions to total energy intake. Women presented with greater levels of dyslipidaemia compared with men but Vitale et al did not detect associations between blood lipids and level of dietary guideline adherence [356]. However, data was only cross-sectional in nature and diet self-reported via FFQ; a measure known to be affected by a high degree of measurement error [137]. Associations between the 'obesogenic' dietary pattern and blood lipids have not been explored in this thesis. A dietary pattern in control-group participants of the prospective Swedish Obese Subjects (SOS) Study [394] used similar RRR intermediates of energy-density, saturated fat (SFA) and fibre, producing an energy-dense, high-SFA, low-fibre dietary pattern. This pattern associated longitudinally with increases in total cholesterol, independent of weight differences and lipid-lowering medication use. Given only minor associations between the 'obesogenic' pattern and weight were identified within Early-ACTID (section 3.4.6), there is very little

evidence to suggest the average differences in 'obesogenic' pattern scores between men and women would be clinically significant.

Within Early-ACTID, dietary pattern changes made by both sexes were largest during the first 6 months of the intervention but were relatively small and were not maintained over the longer-term. In a prospective analysis of dietary pattern change in 2,037 control group participants (13% with T2DM [395]) of the SOS Study mentioned above, Johns et al [396] observed moderate dietary pattern tracking over time in a similarly RRR-derived energy-dense, high-SFA, low-fibre pattern. Control group participants had received no standardised dietary intervention. Evidence indicated tracking was moderate only due to changing intakes of 'unhealthy' foods such as 'fast food' and 'candy' over time, thought to be as a result of repeated attempts at weight loss [396]. Although diet pattern trajectories were observed to be non-linear during the first 2-years of the SOS study, subsequent 5 year changes in average pattern scores were approximately 1.5 SD [396]. This is in line with the magnitude of total dietary pattern change observed during the 1-6y follow-up period in Early-ACTID. Separate studies have also found moderate tracking of the energy-dense, high-fat, low-fibre, 'obesogenic' dietary pattern in children and adolescents [397]. However, the current analysis is the first to explore the 'obesogenic' dietary pattern in adults with T2DM and provides novel insight into how dietary patterns might typically change over both the short- and long-term following non-prescriptive dietetic advice.

This study could not assess the effectiveness of non-prescriptive, patient-centred dietary interventions versus other types of dietary intervention. Whether different approaches benefit dietary change or subsequent maintenance of change in one sex versus the other is currently unclear [387]. Reported changes within Early-ACTID and its follow-up may reflect what is realistically achievable using a non-prescriptive approach under 'real-world' conditions over both the short- and long-term. Although both sexes reported reduced energy intakes compared to baseline at all later timepoints, neither sex reported reaching proposed healthy eating targets for average energy-density of foods (~5.23kJ/g) [398] or fibre-density (3-4g/MJ) [399]. For effective T2DM management, alternative approaches may thus be necessary for maximising dietary pattern changes in both sexes, and in turn, for maintaining these changes longer-term; an area currently lacking evidence within nutritional interventions more generally [400].

This study has several strengths. It appears to be the first study exploring short- and long-term dietary pattern change in early T2DM following a patient-centred dietary intervention. The adoption of healthful dietary patterns is a focus of current T2DM nutritional guidelines, and this study offers

insight into the potential degree of achievable change in men and women separately. It should be highlighted however, that although the Early-ACTID intervention reflects an approach common to current clinical practice, participants received a greater number and length of appointments than typically available in primary care. Secondly, differences in diet trajectories were assessed at multiple levels; individual nutrient change, total energy intake change and combined nutrient and food intake changes in the form of dietary pattern change; all of which led to the same conclusions. Thirdly, dietary patterns were derived using reduced-rank regression. Dietary patterns derived using this method explain maximal variation in grouped rather than single nutrient intakes, offering a compromise for investigating real-world changes in multiple disease-relevant nutrients simultaneously. Fourth, estimates were derived through linear spline multilevel models, allowing the estimation of non-linear trajectories within the contexts of the intervention and its subsequent follow-up. Fifth, diet was measured using four-day food diaries. This method has been found to be less affected by self-report bias compared to other measures such as food frequency questionnaires and 24-hour recalls [139, 140]. Sixth, these higher-quality measures of diet were recorded at multiple timepoints across 6 years, allowing both short- and long-term dietary changes to be explored.

Several limitations of this study should also be noted. First, there is potential selection bias between those who returned food diaries (our analysis sample) versus all those who received the dietary intervention. Those included within our analysis had lower starting weights and lost more weight over 0-6m. It is therefore possible the dietary changes reported by our sample were greater than that of the whole intervention cohort, potentially exaggerating the average level of change, albeit small, achieved by the intervention. However, neither sex nor dietary pattern scores were associated with predictors of dietary data missingness patterns, suggesting those included in our analysis sample but who had varying numbers of dietary measures were not different to one another. Dietary data was therefore considered missing at random within the analysis sample, meeting requirements of the multilevel model. Secondly, due to demographic characteristics, study results are mainly generalisable to white populations living in less socially deprived areas. Males and females within the analysis sample also differed in certain characteristics which may have affected observed dietary pattern change. Females at baseline were slightly younger, less physically active, lived in slightly more deprived areas, had higher BMI and under-reported energy intake to a lesser degree than males. However, higher BMI and lower age and physical activity in females has been observed in other cohorts with T2DM [33, 401] and may therefore simply represent common sex-differences that exist in UK populations newly-diagnosed with T2DM. Third, male and female group sizes were unequal, with approximately 50% more men than women. A higher ratio of men to

women is however common in trials involving people with T2DM [402], potentially as a result of slightly higher prevalence of T2DM in men [5]. Fourth, the majority of dietary data came from the first three timepoints during 0-12 months, with a marked drop in sample size at 3-years in particular. Although the proportion of males and females remained largely consistent across timepoints, the ability to assess long-term dietary pattern trajectories post-intervention is limited. Additionally, interim measures of diet at 2-, 4- and 5-years after baseline were unavailable for analysis for detecting potential sex-differences in dietary change trajectories over the follow-up period. Finally, not all dietary changes made by participants were likely to be captured within the 'obesogenic' dietary pattern scores. The Early-ACTID intervention was not designed to alter adherence to this specific dietary pattern. As detailed in the introduction (section 4.1), previous analyses indicated 0-6m intakes of multiple food groups changed differentially by sex [376], albeit being at risk of potentially spurious findings due to multiple testing. However, these particular food groups did not load highly onto the 'obesogenic' dietary pattern scores and would thus have had little impact on how these dietary pattern scores were observed to change over time.

4.5 Conclusions

Analysis of dietary change at multiple levels of measurement provided no evidence to suggest that non-prescriptive, patient-centred dietary interventions in early T2DM need to be tailored further by sex. Dietary interventions in early T2DM should remain tailored to initial diet quality, in line with current practice.

4.6 Implications for thesis

Findings from study 2 demonstrate that a non-prescriptive, patient-centred dietary intervention representing typical UK dietetic practice produces similar dietary pattern changes in both men and women. Any dietary behavioural differences that may typically exist between men and women more generally do not appear to impact responses to non-prescriptive dietary advice provided in early T2DM. The magnitude of change in dietary patterns were however small in both sexes and was unable to be maintained over the longer-term. Dietetic advice has been demonstrated to improve dietary patterns in the direction of this advice within study 1 and 2, but subsequently maintaining

such changes long-term potentially requires a more intensive or longer dietary intervention than that provided within the Early-ACTID trial. If dietary patterns are found to associate with delaying or preventing disease progression in T2DM, being able to maintain long-term change in dietary patterns is likely to be key. Whether such associations between dietary pattern and long-term glycaemic deterioration indeed exist will now be explored within studies 3 and 4 (Chapter 5 and Chapter 6 respectively).

Chapter 5 - Study 3: Dietary patterns and glycaemic deterioration in participants of the Early-ACTID trial

5.1 Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease characterised by declining beta-cell function over time [15]. This manifests clinically as deteriorating glycaemic control and need for escalating drug intervention [16, 17]. In turn, an inability to maintain blood glucose levels within appropriate limits leads to an increased risk of long-term micro- and macro-vascular complications [403]. However, the rate at which glycaemic control deteriorates, and hence how disease progresses, is found to be highly variable amongst individuals [15, 18], with current research focussed on finding factors that could be used to delay or prevent deterioration over the longer-term [404]. Amid increasing global prevalence [5] and the negative impact managing T2DM has on healthcare costs [12] and individual quality of life [13, 14], finding those factors that might be able to delay progression of T2DM remains a leading societal concern.

Disease progression in T2DM has been defined and measured in various ways [15, 91] (see section 2.4.1). Typically, it has been measured through the time to either initiation or intensification of glucose-lowering medications, or by the reaching of specific glycaemic thresholds [91]. However, this 'time to failure' approach is notably limited in its disregarding of partial progression towards failure [104]. It also ignores potential real world effects of clinical inertia [102, 103], whereby the time at which a medication is initiated or increased in dose lags behind when it may otherwise be clinically indicated. To avoid such issues, an alternative approach has been to derive a so-called 'coefficient of failure' [104], representing the rate at which glycaemia deteriorates over time, usually in terms of increases per year in HbA1c after accounting for glucose-lowering medication use. This method has typically been used in a monotherapy context [17, 104, 114–117], but more recently under conditions of changing combination therapy [18, 118]. Kahn et al [17] derived mean rates of HbA1c deterioration on constant metformin monotherapy of 1.5 mmol/mol (0.14%) per year over a median four years, with HbA1c measured every 2-3 months, in n=1,454 US, Canadian and European participants of A Diabetes Outcome Progression Trial (ADOPT). Wallace et al [104] calculated mean HbA1c deterioration over time under constant sulphonylurea monotherapy as 3.7-5.5 mmol/mol (0.34-0.50%) per year over 10 years, with HbA1c measured annually, in n=129 of the Oxford cohort

of the UK Prospective Diabetes Study (UKPDS). Under combination therapy, Bizzotto et al [118] derived mean BMI- and multiple medication-adjusted rates of HbA1c deterioration of 0.69 mmol/mol (0.06%) per year over 3 years, with HbA1c measured every 9-18 months, in N=625 of the European observational Diabetes Research on Patient Stratification (DIRECT) 2.2 study [118] (see also analyses presented in Chapter 6). Donnelly et al [18] derived a mean rate of BMI- and multiple medication-adjusted HbA1c deterioration of 1.4 mmol/mol (0.12%) per year over 9.4 years, with a median of 21 HbA1c measures per individual, from observational electronic medical record data from 1994 onwards in 5,342 Scottish people [18]. All participants in the above trials had been recently-diagnosed with T2DM (varying in definition from 0 to 3 years duration [17, 18] at study baselines).

A recent systematic review identifying predictors associated with faster T2DM progression from 61, mostly observational cohort studies [91] (discussed previously in section 2.4.2), found that consistent phenotypic predictors were high baseline HbA1c, younger age at diagnosis, high baseline adiposity (measured as weight, BMI or waist circumference), baseline dyslipidaemia (low HDL, high LDL and high triglycerides), and low baseline beta-cell function; as measured by homeostasis model assessment (HOMA2-%B) [91]. Predictors associating with glucose-lowering medication- and BMI-adjusted rates of glycaemic deterioration derived previously in the DIRECT 2.2 observational study were found to be high visceral or liver fat, deteriorating insulin sensitivity, beta-cell function and dyslipidaemia, and increasing endogenous insulin clearance by the liver [118] (data from the DIRECT 2.2 study is explored further in Chapter 6). The Diabetes Remission Clinical Trial (DiRECT) (see section 2.3.2.1) showed that significant weight loss (>15kg) soon after diagnosis also appears able to strongly arrest disease progression to the point of accomplishing disease remission, provided such weight loss can be maintained [70, 71]. While several phenotypic factors have therefore been associated with faster T2DM progression, the effect of dietary pattern on rates of glycaemic deterioration remains largely unexplored.

As highlighted throughout this thesis, diet remains one of the cornerstones of T2DM management [20, 21]. Weight loss appears to be the primary mechanism for improving glycaemic control and other cardiovascular risk factors in T2DM [22]. Outside of clinically-managed, very-low calorie diets for achieving dramatic weight loss [70], a range of dietary approaches have been demonstrated as suitable for aiding weight loss and achieving the associated benefits, such as the Mediterranean, DASH and other predominantly plant-based dietary patterns [20, 289]. Low-carbohydrate diets [199] are also considered suitable over at least the short-term (<12 months), although long-term benefits remain unclear [405] (see section 2.7.1.1.3). However, the majority of current literature has studied

the effects of diet on glycaemic control over only short timescales (≤1 year); which is representative of glycaemic effects attributed to lifestyle change but insufficient for assessing associations with longer-term glycaemic deterioration because of progressing disease. In addition, co-occurring weight loss and glucose-lowering medication changes in many studies [288] are insufficiently recorded or accounted for, rendering it difficult to identify potentially independent effects of diet.

Only 3 studies have explored associations between diet and long-term glycaemic deterioration in T2DM [98, 118, 290] (previously discussed in sections 2.7.2.2 and 2.7.3.1). A four-year randomised controlled trial (RCT) by Esposito et al [97] compared the effects of a Mediterranean-style diet (<50% energy from carbohydrates, n=108) and a low-fat diet (<30% energy from fat; n=107), either on the time to requiring glucose-lowering medications or when HbA1c surpassed 53 mmol/mol (7%) in early T2DM. Those randomised to the Mediterranean-style diet saw greater delays in requiring medications compared to those following the low-fat diet (44% versus 70% on medications at 4 years respectively) [97]. Follow-up analyses revealed median time to medication initiation was 4.8 years in the Mediterranean-style diet group and 2.8 years in the low-fat diet group [98], suggesting potential benefits of the Mediterranean dietary pattern on delaying glycaemic deterioration in T2DM. However, cumulative between-group weight differences over the study were found to be greater in the Mediterranean-style diet group [98], potentially explaining some of these differences. The latter point remains an important detail when seeking to provide patients with the most appropriate dietary advice for managing their condition and for helping minimise any patient anxieties around the specifics of dietary intake.

The five-year PREDIMED trial investigated effects on cardiovascular disease prevention with an *ad libitum* Mediterranean diet supplemented with either nuts or extra-virgin olive oil (EVOO) compared with an *ad libitum* low-fat diet [296] (previously discussed in section 2.7.3.1). Secondary analyses in 1,210 participants with T2DM at baseline (unspecified duration) by Basterra-Gortari et al. [290], indicated that the Mediterranean diet supplemented with EVOO (n=447) delayed the need for glucose-lowering medications (adjusted Hazard ratio: 0.78 [95%CI: 0.62, 0.98]) versus the low-fat diet (n=369) after a median 3.2 years. No differences between diets were found in the time to initiating insulin and no differences in time to medication initiation were found for the Mediterranean diet supplemented with nuts compared to the low-fat diet [290]. Weight change differences between groups within the analysis sample were left unexplored, again leaving the specific effects of diet on glycaemic deterioration unclear. As also highlighted in section 2.7.3.1, PREDIMED data quality has been called into question due to issues relating to incomplete randomisation of participants [299]. Although the secondary analysis by Basterra-Gortari et al.

aimed to take these randomisation issues into account statistically, caution should be taken when interpreting results arising from this dataset.

Only one study claims to have directly explored associations between a 'dietary pattern' and rates of glycaemic deterioration in early T2DM. In analysis of data from the 3-year DIRECT 2.2 observational study by Bizzotto et al [118], an *a priori* dietary index score was used to assess adherence to select components of UK healthy eating guidelines (total carbohydrate, sugar, fat, SFA, salt, dietary fibre, fruit and vegetable intakes and total fish intake) [118, 303]. No associations with BMI- and glucose-lowering medication-adjusted rates of HbA1c deterioration were found with either individual nutrient intakes or the diet index scores [118]. However, although the index scores were labelled as 'dietary pattern' scores, the index scores predominantly reflected summated individual nutrient intakes only, thus failing to assess combined nutrient and food intakes [148]. Additionally, diet was assessed at only a single point in time (baseline). The scoring of dietary intakes against an *a priori* index also has notable disadvantages. It cannot discern intakes between individuals with intermediate index scores [406], and importantly, may not capture the specific dietary intake variation most relevant to the specified outcome; in this case, glycaemia. A data-driven approach that is able to maximally explain variation in nutrients potentially intermediate between diet and glycaemic outcomes, such as with reduced-rank regression, offers a potentially novel way to assess such associations. A data-driven 'carb/fat balance' dietary pattern was associated with improved glycaemic control independent of weight change in analysis of 0-6 months of the Early-ACTID trial (see Chapter 3). It is unknown if such a pattern relates to longer term HbA1c deterioration.

In this study, associations between a 'carb/fat balance' dietary pattern and long-term HbA1c deterioration will be explored using data from participants of the Early-ACTID trial and its five-year follow-up. This serves as an extension of analyses presented in study 1 (Chapter 3), which explored associations between short-term change in both dietary patterns and HbA1c during the trial only. As far as the author is aware, this is the first study to explore associations between data-driven dietary patterns and long-term glycaemic deterioration in established T2DM.

5.2 Methods

5.2.1 Sample

Data came from participants of the Early-ACTID trial [326] and who consented to take part in its five-year post-intervention follow-up study. Further description of the Early-ACTID trial can be found in sections 3.3.1 and 3.3.2. Participants who consented to take part in follow-up (N=476) were invited to annual consultations for usual care and monitoring by trial clinicians for a further five-years.

5.2.2 Dietary data

Diet data from all available timepoints (0-, 6-months, 1-, 3- and 6-years) were included in the current analysis. Further description of collected dietary data and its coding can be found in (section 3.3.3).

5.2.3 'Carb/fat balance' dietary pattern derivation

Data on 'carb/fat balance' dietary patterns derived via reduced-rank regression (RRR) from 4-day food diary data at baseline were used to generate equivalent dietary pattern scores at follow-up timepoints (6 months, 1 year, 3 years and 6 years) using the methods described in section 3.3.4. Higher 'carb/fat balance' dietary pattern scores were associated with greater consumption of fresh fruit, low-fat milk, boiled/baked potatoes and legumes, while also eating less higher-fat processed meats, butter/animal fats, red meat, and low-fibre bread (Figure S8.1).

To assess what a 1-SD change in 'carb/fat balance' dietary pattern score means at each timepoint, nutrient intake changes relating to a 1-SD increase in dietary pattern score were calculated at each timepoint using a series of simple linear regressions, with 'carb/fat balance' dietary pattern score as predictor and either fibre-density or percentage energy from total carbohydrate, starches and sugars, total fat, SFA, MUFA or PUFA as separate outcomes.

5.2.4 Misreporting of energy intake

Misreporting status was assessed and assigned at baseline, 3- and 6-years as described in sections 3.3.5 and 4.2.3, producing a binary categorical variable (under-reporter and plausible-reporter) for each timepoint. As under-reporting status was found to be stable over time (intraclass-correlation

coefficient (ICC) from a random intercept logistic multilevel model: 0.98), only baseline under-reporting status was used as a variable in subsequent analyses.

5.2.5 Covariates and other measures

Description of other recorded measures in the ACTID sample can be found in section 3.3.6. To maximise analysis power, multiple glucose-lowering medications were combined into a single variable. The sum of the percentage of maximum doses (Table S8.22) for non-metformin/insulin medications (sulphonylureas, glitazones, GLP1 agonists, acarbose, and DPP4 inhibitors) was computed (range 0-500%). Covariates used for this analysis were baseline age, sex, smoking status, total physical activity and energy under-reporting status, and timepoint-specific bodyweight, TEI, whether taking any insulin and percentage of maximum dose of 1) metformin and 2) non-metformin/insulin glucose-lowering medications.

5.2.6 Statistical analysis

Variables were described with the use of mean (SD) if approximately symmetrical or median (quartile 1, quartile 3) otherwise. Random slope multilevel models with repeated measurements (level 1) nested within participants (level 2) were used to examine HbA1c (outcome) trajectories over time. As stated in section 4.2.5, multilevel models estimate mean trajectories of a specified outcome over time and account for the intra-person dependency of measurements over time. Participant data is included at timepoints where there is complete predictor, outcome and covariate data. Any missing data in these variables at a given timepoint will lead to removal of all data for that individual at that specific timepoint. A balanced dataset across time is not required and individuals who contribute fewer than the maximum number of observations are retained under a Missing At Random (MAR) assumption [381]. Modelling random slopes allows for mean differences between participants in HbA1c concentrations to vary over time, in line with differing rates of glycaemic deterioration observed amongst individuals with T2DM [18, 92, 101]. Trajectories for HbA1c over time were modelled linearly in line with previous findings that glycaemic deterioration typically follows a linear trajectory [18, 92, 101]. Further information on specific modelling decisions is provided in Information S8.7.

To identify how variation in dietary pattern scores over time compared between-persons (from one person to another) versus within-persons (from one timepoint to another), an intraclass correlation coefficient (ICC) was calculated from a linear empty means, random intercept model, with no exposures and with dietary pattern scores as the outcome. The ICC for dietary pattern scores was 0.43, meaning 43% of variation in dietary pattern score change over 0-6y was between-persons and 57% was within-persons (Information S8.7). Therefore, to differentiate associations between cross-sectional (between-person) or longitudinal (within-person) dietary pattern score change and HbA1c concentrations, dietary pattern scores were disaggregated into between- and within-person components through person-mean centring [381]. Specifically, pattern scores were split into a time-invariant variable for the person-mean (i.e. average pattern score across all timepoints) and a time-varying deviation from the person-mean score at each given timepoint. These two variables i.e. individual mean dietary pattern and timepoint-specific individual deviation from their own mean dietary pattern, represent the different sources of variation inherent within the dietary pattern scores and were both added to models as individual predictors. As there were no indications that dietary pattern scores varied randomly over time (see Information S8.7), disaggregating between- and within-person effects in this way does not introduce bias into dietary pattern estimates [381]. Glucose-lowering medications, total energy intake and bodyweight were similarly disaggregated into their between- and within-person components via person-mean centring (Information S8.8).

Average dietary pattern change was found to vary in direction across different periods of the Early-ACTID trial (see section 3.4.4). Therefore, the disaggregated dietary pattern score trajectories were modelled using a linear spline for periods 0-6m, 6-12 months (6-12m) and 1-6 years (1-6y), with pattern score interactions with each of these time-periods serving as exposures in each model. The primary estimates of interest within each model were the interaction between disaggregated dietary pattern scores and the 1-6y time-period. Data from all time-periods were included within each analysis model in order to maximise use of available data and to adjust for differences between participants prior to the 1-6y follow-up period as fully as possible. Measurement times were modelled as continuous to account for measurement time variation during each measurement wave, with spline breakpoints after 6-months and 12-months set to median measurement values; 0.58 years (6.9 months) and 1.07 years (12.8 months) respectively.

A series of multilevel models were used to assess whether dietary pattern scores associated with HbA1c change over time, in line with the general analysis structure used in Study 1 (see section 3.3.7): *Model 1* estimated the associations between dietary pattern score interactions with time (exposure) and glucose-lowering medication-adjusted HbA1c (outcome). Predictors in *Model 1* were

time, person-mean dietary pattern score and its interactions with each time period, timepoint-specific deviation from person-mean dietary pattern score and its interactions with each time period, and disaggregated between/within person glucose-lowering medications and their interactions with time. *Model 2* estimated the dietary pattern and time-period interaction associations with medication-adjusted HbA1c independent of potential confounders by adding to *Model 1:* baseline age, sex, smoking status, total physical activity level and energy under-reporting status and each of their interactions with time. *Model 3* estimated potential mediation by adding disaggregated between- and within-person energy intakes and bodyweight (potential mediators) and their interactions with time to model 2. Units of dietary pattern score between- or within-person effect estimates on HbA1c within models 1-3 were 1-SD per 6 months for an SD of baseline dietary pattern score. Finally, to obtain estimates of overall change in medication-adjusted HbA1c during the 1-6 year period, *Model 1* was repeated without adjustment for dietary pattern scores and with the time predictor replaced by time-period.

All models were run using maximum-likelihood estimation. To assess validity of results from *Model 3*, graphical diagnostics were performed to assess assumptions of residual normality and homoscedasticity (over time and over predicted values for HbA1c) (Figure S8.13). Evidence of association was considered when $p<0.05$ for the dietary pattern by time-period interaction terms and the strength of evidence assessed by interpreting the clinical relevance of their β and 95%CI.

5.2.7 Sensitivity Analyses

Computing dietary pattern scores at 3 and 6 years based on baseline pattern loadings assumes that the pattern structure (i.e. the size or direction of food group loadings for pattern scores) is broadly consistent over time. To check consistency in the 'carb/fat balance' pattern structure, the RRR was repeated independently at 3 and 6 years. The first pattern derived using RRR at 3 and 6 years were compared with the first pattern derived previously at baseline using Tucker's congruence coefficient (CC) [342]. A CC>0.85 was taken to indicate dietary patterns were structurally similar between timepoints [342].

In *Model 1a*, we estimated the impact of having missing covariate data on *Model 1* estimates by repeating *Model 1* in a restricted sample that had complete data on all covariates included in models 2-3, replicating methods used in Study 1 (Information S8.2). The effects of missing data versus

confounder adjustment were differentiated by comparing changes in the β and 95% CI in models 1 to 1a and models 1a to 2.

To assess the extent of bias in model estimates due to missing HbA1c (outcome) data across time, two dichotomous HbA1c missingness pattern indicators were created and assessed for association with main model exposure (dietary pattern score) and outcome (HbA1c) at each separate timepoint using simple logistic regression. Missingness pattern indicator 1 was assigned (=1) for sustained study attrition or to those who declined to take part in follow-up. Missingness pattern indicator 2 represented all other missingness patterns not explained by indicator 1 (=1) (Table S8.23). To estimate potential selection bias, differences in baseline characteristics were compared between those in our analysis sample and all those who took part in Early-ACTID.

Analyses were performed in Stata (v15; StataCorp LLC, College Station, TX, USA), with the RRR procedure incorporating SAS (v9; SAS Institute, North Carolina, USA) (see Information S8.3).

5.3 Results

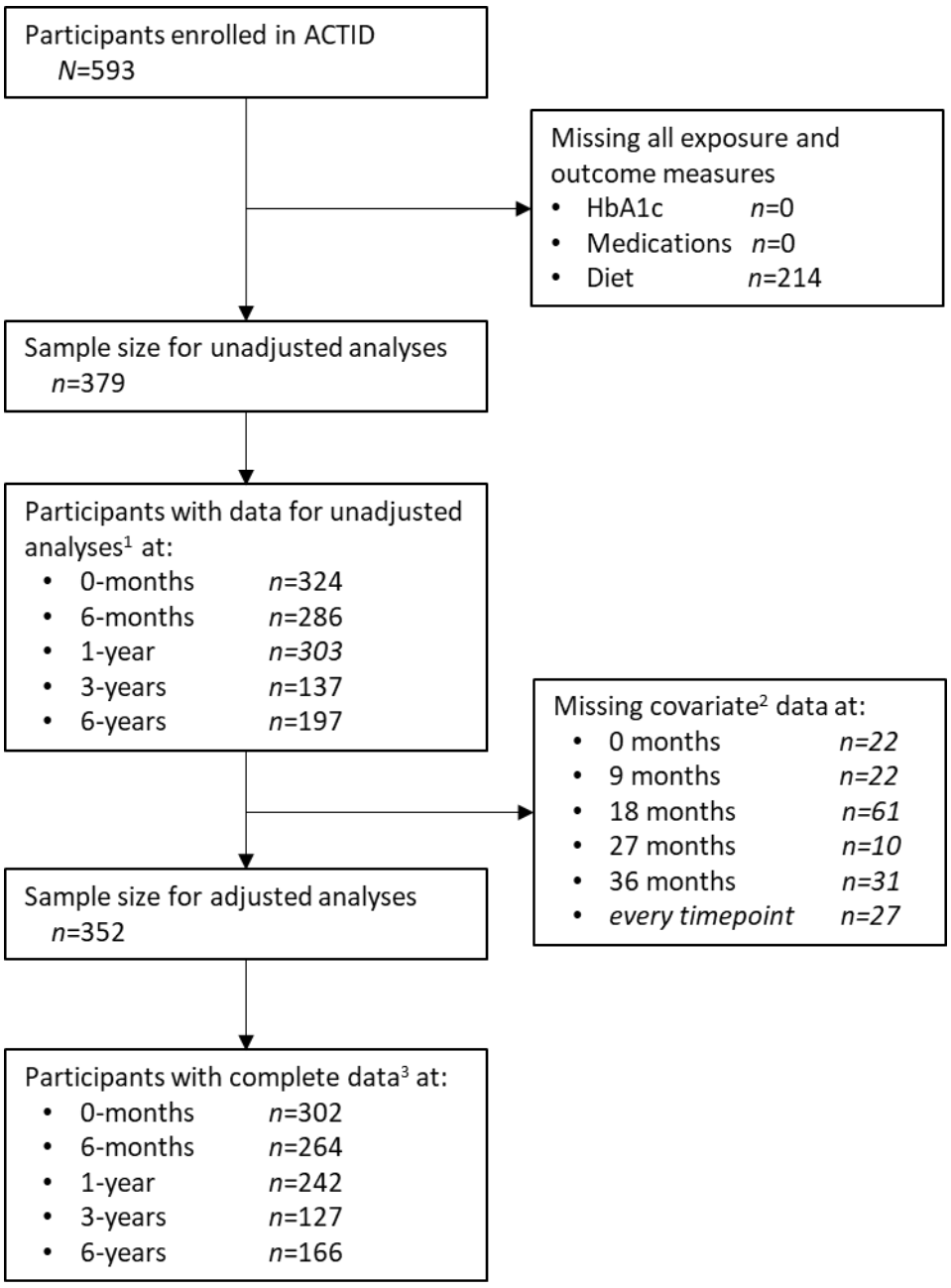
5.3.1 Sample characteristics

Data for adjusted models 1a-3 were available in n=352 participants (59% of those enrolled at baseline) (Figure 5.1). Complete data was available at each individual timepoint in n=302, n=264, n=242, n=127 and n=166 participants at 0-, 6-months, 1-, 3- and 6-years respectively (Figure 5.1), with a median (quartile 1, quartile 3) number of datapoints per person across the study of 3 (2, 5). Participants with a complete set of data available at baseline (n=302) were more likely to be male (67%) with median age 62 years, bodyweight 86.6kg, BMI 29.4kg/m^2, HbA1c 46 mmol/mol (6.4%), with 34% taking metformin and 10% taking non-metformin/insulin medications (Table 5.1). Participants with data available for inclusion in models 1a-3 for 3- and 6 years compared with those at baseline were more likely to be male (70-72% vs 67%) and were slightly older (median 63 vs 62 years) (Table 5.1), but were otherwise similar. Raw HbA1c concentrations and the number of participants requiring glucose-lowering medications both increased between 1-6 years (46-50 mmol/mol (6.4-6.7%); 39-60% on metformin; 10-23% on non-metformin/non-insulin medications; 0.4-3% on insulin) (Table 5.1). Dietary intakes at each timepoint for participants included in models 1a-3 are presented in Table 5.2. A 1-SD 'carb/fat balance' dietary pattern score change was

associated with a broadly similar degree of change in fibre-density and percentage energy from starches/sugars and fat intakes at each timepoint (Table 5.3).

Compared to all Early-ACTID participants (N=593), participants included in models 1a-3 (n=352) at baseline were slightly older (median 62 vs 61 years), had lower bodyweight and BMI (86.9 vs 89.0 kg; 29.5 vs 30.4 kg/m^2), and had lower beta-cell function (HOMA2-%B; 77% vs 84%) and insulin resistance (HOMA2-IR; 4.6 vs 4.9) but were otherwise similar (Table S8.24).

Figure 5.1 Sample size flow chart.



[1] Participant data that is complete at a given timepoint is retained within a multilevel model. Any missing data in either predictor, outcome or covariate at a given timepoint will lead to removal of all data for that individual at that specific timepoint only. Data is therefore not required to be balanced over time. [2] baseline age, sex, smoking status, total physical activity, energy under-reporting status, timepoint-specific bodyweight and energy intake. [3] complete data for baseline age, sex, smoking status, total physical activity, energy under-reporting status, and timepoint-specific bodyweight, energy intake, HbA1c, glucose-lowering medications and dietary pattern score.

Table 5.1: Characteristics of participants included in Models 1a-3 (N=352) at each timepoint.

	0 months	6 months	1 year	3 years	6 years
n (% of N=352)	302 (86%)	264 (75%)	242 (69%)	127 (36%)	166 (47%)
Male	201 (67%)	177 (67%)	168 (69%)	92 (72%)	116 (70%)
Baseline age (years)	62 (56, 69)	62 (56, 69)	62 (56, 69)	63 (59, 69)	63 (58, 68)
Baseline disease duration (years)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)
Baseline IMD score at baseline	12.6 (6.5, 18.9)	12.7 (6.5, 18.9)	12.4 (6.3, 18.9)	12.6 (6.2, 18.7)	12.7 (6.3, 18.7)
Baseline smoker	20 (7%)	19 (7%)	16 (7%)	11 (9%)	12 (7%)
Baseline total physical activity (cpm)	290 (221, 364)	291 (222, 365)	294 (226, 373)	303 (234, 373)	294 (227, 367)
Baseline MVPA (mins/day)	21 (12, 36)	21 (13, 36)	22 (11, 37)	25 (14, 39)	22 (14, 38)
Weight (kg)	86.6 (77.6, 95.8)	84.7 (75.6, 94.4)	85.0 (77.0, 94.0)	83.8 (75.3, 93.3)	83.6 (74.0, 93.7)
BMI (kg/m^2)	29.4 (27.2, 33.0)	28.8 (26.4, 32.6)	28.7 (26.4, 32.7)	28.0 (25.8, 32.2)	28.7 (26.2, 32.1)
HbA1c (mmol/mol)	46 (42, 52)	45 (41, 52)	46 (41, 53)	49 (44, 56)	50 (45, 57)
HbA1c (%)	6.4 (6.0, 6.9)	6.3 (5.9, 6.9)	6.4 (5.9, 7.0)	6.6 (6.2, 7.3)	6.7 (6.3, 7.4)
HOMA2-%B	76 (51, 117)	74 (49, 110)	75 (53, 111)	66 (48, 100)	64 (43, 96)
HOMA2-IR	4.5 (3.0, 6.9)	3.7 (2.5, 5.8)	4.2 (2.6, 6.1)	4.2 (2.7, 7.2)	4.1 (2.8, 6.9)
On metformin	103 (34%)	92 (35%)	95 (39%)	63 (50%)	101 (60%)
Metformin (%max dose)	0 (0, 33)	0 (0, 33)	0 (0, 33)	0 (0, 50)	33 (0, 57)
On non-metformin/non-insulin medications	29 (10%)	28 (11%)	25 (10%)	22 (17%)	39 (23%)
Non-metformin/non-insulin medications (%max dose)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
On insulin	0 (0%)	0 (0%)	1 (0.4%)	2 (2%)	5 (3%)

Data presented as median (quartile 1, quartile 3) or n(%). *BMI – body mass index; cpm – counts per minute; MVPA – moderate-to-vigorous physical activity; IMD – Index of Multiple Deprivation; HOMA2-%B – Homeostasis model assessment 2 of beta-cell function; HOMA2-IR – Homeostasis model assessment 2 of insulin resistance.*

Table 5.2: Diet characteristics for sample included in models 1a-3 at each timepoint.

		0 months	6 months	1 year	3 years	6 years
n (% of N=352)		302 (86%)	264 (75%)	242 (69%)	127 (36%)	166 (47%)
Carb/fat balance dietary pattern score		0.04 (-0.53, 0.49)	0.14 (-0.30, 0.65)	0.08 (-0.47, 0.62)	0.06 (-0.54, 0.55)	-0.15 (-0.59, 0.39)
Energy intake (kJ)		7347 (6146, 8591)	6562 (5523, 8104)	6212 (5219, 7473)	6771 (5679, 8086)	6623 (5599, 7838)
Total carbohydrate (%TEI)		45.4 (40.6, 49.8)	45.7 (42.2, 50.8)	45.5 (40.9, 50.0)	44.4 (40.5, 49.2)	42.7 (39.1, 47.4)
Starches and sugars (%TEI)		43.5 (39.1, 47.8)	44.0 (40.3, 48.8)	43.5 (39.3, 47.8)	42.6 (38.8, 47.2)	41.1 (37.7, 45.4)
Fibre (g/MJ)		2.2 (1.8, 2.6)	2.4 (2.0, 2.9)	2.4 (1.9, 2.8)	2.2 (1.8, 2.6)	2.2 (1.8, 2.6)
Protein (%TEI)		17.9 (16.0, 20.0)	18.5 (16.5, 20.4)	18.8 (17.0, 20.9)	17.6 (16.4, 20.2)	18.2 (16.0, 20.6)
Total fat (%TEI)		33.8 (30.2, 37.4)	33.4 (29.9, 38.1)	33.1 (28.6, 36.7)	33.6 (30.6, 38.0)	35.1 (31.8, 38.7)
SFA (%TEI)		11.0 (9.4, 13.2)	10.7 (9.1, 13.2)	10.5 (8.7, 13.3)	11.3 (9.7, 13.5)	11.7 (10.0, 14.9)
MUFA (%TEI)		12.1 (10.5, 13.7)	12.3 (10.6, 13.8)	11.7 (9.6, 14.1)	12.0 (10.5, 14.3)	12.5 (10.8, 14.3)
PUFA (%TEI)		6.5 (5.3, 7.9)	6.7 (5.5, 7.7)	5.3 (4.0, 6.5)	5.3 (4.0, 6.5)	5.2 (4.0, 6.3)
Alcohol (%TEI)		2.9 (0.0, 7.8)	1.9 (0.0, 6.9)	1.6 (0.0, 6.1)	1.4 (0.0, 5.9)	1.7 (0.0, 5.9)
Baseline energy under-reporters		127 (42%)	112 (42%)	100 (41%)	48 (38%)	67 (40%)
Highest positive loading food groups						
Fruit (fresh), g/d		157 (90, 236)	152 (90, 236)	159 (93, 234)	129 (75, 223)	114 (64, 208)
	% consumers	93	94	94	97	89
Low fat milk, g/d		180 (110, 250)	169 (93, 251)	147 (72, 232)	193 (119, 276)	168 (101, 260)
	% consumers	92	95	95	96	93
Boiled/baked potatoes, g/d		44 (0, 78)	46 (24, 85)	45 (23, 74)	46 (15, 89)	45 (0, 76)
	% consumers	71	77	82	80	75
Legumes, g/d		18 (0, 45)	19 (0, 44)	18 (0, 46)	15 (2, 41)	15 (0, 36)
	% consumers	69	70	70	76	72
Meat substitutes, g/d		0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	% consumers	2	2	2	4	4
Highest negative loading food groups						
Higher fat processed meats, g/d		10 (0, 30)	10 (0, 24)	6 (0, 25)	9 (0, 23)	13 (0, 30)
	% consumers	57	56	55	53	63
Butter & animal fats, g/d		0 (0, 0)	0 (0, 0)	0 (0, 3)	0 (0, 5)	0 (0, 6)

	% consumers	23	23	31	35	36
Red meat, g/d		17 (0, 34)	15 (0, 37)	9 (0, 20)	10 (0, 28)	10 (0, 27)
	% consumers	55	57	59	59	62
Low fibre bread, g/d		0 (0, 38)	0 (0, 23)	18 (0, 53)	0 (0, 45)	16 (0, 39)
	% consumers	49	37	58	47	57
Fried/roast, chips & other potato with added fat, g/d		38 (0, 69)	27 (0, 53)	30 (0, 61)	31 (0, 64)	33 (0, 63)
	% consumers	69	61	62	66	71

Data presented as median (quartile 1, quartile 3) or n(%). *TEI – total energy intake; SFA – saturated fat; MUFA – monounsaturated fat; PUFA – polyunsaturated fat.*

Table 5.3: Nutrient intake changes for a 1-SD increase in 'carb/fat balance' dietary pattern score at each individual timepoint.

Values are beta's from simple linear regressions with diet pattern score as predictor and individual nutrient as outcome.

Timepoint	Total carbohydrate (%TEI)	Starches/sugar (%TEI)	Fibre density (g/MJ)	Total fat (%TEI)	SFA (%TEI)	MUFA (%TEI)	PUFA (%TEI)
0 months	7.0	6.6	0.5	-4.9	-2.6	-2.0	-0.3
6 months	7.0	6.6	0.5	-5.7	-3.1	-2.1	-0.1
1 year	6.1	5.7	0.5	-5.6	-2.7	-2.3	-0.3
3 years	6.3	5.9	0.5	-5.5	-2.5	-2.1	-0.5
6 years	5.6	5.2	0.5	-5.0	-2.6	-2.0	-0.3

TEI – total energy intake; SFA – saturated fat; MUFA – monounsaturated fat; PUFA – polyunsaturated fat.

5.3.2 Carb/fat balance dietary pattern scores did not associate with HbA1c deterioration

Medication-adjusted HbA1c was found to increase at a rate of 1.49 [95%CI: 1.01, 1.97] mmol/mol (0.14 [0.09, 0.18] %) per year ($p<0.001$) over the 1-6 year follow-up period. There was no evidence of association between differences in mean 'carb/fat balance' dietary pattern scores and changes in HbA1c during 1-6y (Table 5.4). There was also no evidence that deviation from a person's mean 'carb/fat balance' dietary pattern score was associated with the rate of HbA1c change during 1-6y; i.e. eating a dietary pattern that had more carbohydrates and less fat than what was usual for the individual did not associate with long-term changes observed in their HbA1c. Associations between dietary patterns and HbA1c change observed during periods 0-6m and 6-12m were in accordance with findings presented in study 1 (Table S8.25). Model diagnostics revealed no major issues with residual normality or homoscedasticity (Figure S8.13).

Table 5.4: Between- and within-person associations between differences in 'carb/fat balance' dietary pattern score and HbA1c change over 1-6y.

Between-person β's represent the change in HbA1c per 6 months associated with a 1-SD higher mean dietary pattern score over the course of the study (0-6y). Within-person β's represent the change in HbA1c associated with a 1-SD increase in dietary pattern score above a person's mean dietary pattern score per 6 months.

	1-6y			
Model	**n**	**β**	**95%CI**	**p**
Between-person				
1	379	-0.21	-0.48, 0.06	0.126
1a	352	-0.28	-0.56, 0.00	0.054
2	352	-0.27	-0.56, 0.01	0.061
3	352	-0.26	-0.55, 0.03	0.074
Within-person				
1	379	0.14	-0.19, 0.46	0.403
1a	352	0.12	-0.21, 0.45	0.465
2	352	0.13	-0.19, 0.46	0.416
3	352	0.17	-0.16, 0.51	0.311

1 – Random linear piecewise slope multilevel model for HbA1c (outcome) adjusted for continuous time, disaggregated between- and within-person dietary pattern scores and their interactions with time-period (exposures), disaggregated between- and within-person glucose-lowering medications (metformin dose, non-metformin/insulin dose and insulin use) and their interactions with time.

1a – Model 1 restricted to sample with complete sets of covariate data for ≥1 timepoint.

2 – Model 1a adjusted for baseline sex, age, smoking status, total physical activity and energy under-reporting status (potential confounders) and their interactions with time.

3 – Model 2 adjusted for disaggregated between- and within-person energy intakes and weight (potential mediators) and their interactions with time.

5.3.3 Sensitivity analyses

After running RRR at each timepoint independently, 'carb/fat balance' dietary patterns were found to be structurally similar between baseline and 6-years (CC>|0.85|) but not between baseline and 3-years (CC=|0.78|) (Table S8.27), as found previously in analyses involving the 'obesogenic' dietary pattern (section 4.3.4). There remained no evidence of association between differences in dietary pattern scores (between- or within-persons) and HbA1c change during 1-6y before or after restricting the sample to those with a complete set of covariate data at one or more timepoints (models 1-1a; Table 5.4). Neither dietary pattern scores nor HbA1c concentrations associated with either HbA1c missingness pattern indicator (Table S8.28), indicating missing HbA1c values could be assumed to be MAR and model associations were not being confounded by missing outcome data.

5.4 Discussion

This study examined whether a nutrient-mediated, data-driven dietary pattern associated with long-term glycaemic deterioration in T2DM for the first time. Average medication-adjusted HbA1c concentrations deteriorated by 1.49 mmol/mol (0.14%) per year during five years of follow-up of the Early-ACTID trial. However, there was no evidence that the rate of glycaemic deterioration associated with differences in dietary pattern scores.

Glucose-lowering medication-adjusted HbA1c was found to deteriorate during one to six years of follow-up of the Early-ACTID trial at an average rate of 1.49 mmol/mol (0.14%) per year, in line with average rates of 1.4 mmol/mol (0.13%) per year derived from a much larger sample of people with T2DM in the Genetics of Diabetes Audit and Research in Tayside Study (GoDARTS) by Donnelly et al [18]. The similarity between the derived rates of glycaemic progression in participants of Early-ACTID and by Donnelly et al [18] indicates little evidence that there was a glycaemic after-effect from the Early-ACTID intervention acting on the rate of glycaemic deterioration post-trial. The calculated bounds of the 95%CI in the average rate of HbA1c deterioration during 1-6 years ranged from 1.01 mmol/mol (0.09%) per year to 1.97 mmol/mol (0.18%) per year. Although such increases may not appear clinically significant in themselves, the cumulative effect of such increases in HbA1c over time in the context of ongoing and increasing pharmaceutical intervention are likely to place individuals at significant cardiovascular risk. In one meta-analysis of 26 cohort studies [39], an increase of 11mmol/mol (1.0%) in HbA1c was associated with a 17% increased risk of CVD; a risk potentially applying to participants of Early-ACTID within 5-10 years unless glycaemic progression can be delayed or arrested. However, the current study provides no evidence that changes in dietary patterns that balance carbohydrate and fat intakes would help achieve this.

The current study provided no evidence to suggest that between- or within-person differences in a 'carb/fat balance' dietary pattern score associated with the rate of HbA1c deterioration in early T2DM. There is limited evidence at present on an effect of dietary patterns (that is, the specific combination of foods and nutrients in the diet) on disease progression in T2DM. As highlighted within the introduction to this chapter (section 5.1), rates of medication- and BMI-adjusted HbA1c deterioration derived in previous analysis of the DIRECT 2.2 cohort study [118] failed to associate with diets scored for adherence to UK 'healthy eating' nutrient guidelines [303]. Although these dietary index scores were labelled as dietary pattern scores, they should not be defined as such as they did not inform on the effects of food and nutrient intakes in combination. The remaining evidence for potential benefits of dietary patterns on delaying longer-term rates of T2DM

progression relates to the Mediterranean diet, whereby an RCT by Esposito et al [97, 98] and a secondary analysis of the PREDIMED study [290], both discussed within the chapter introduction (section 5.1), found adherence to a Mediterranean-style dietary pattern delayed the need for glucose-lowering medications in early T2DM. The Mediterranean dietary pattern thus warrants further investigation for potential weight-independent effects on glycaemia, as this currently remains unclear, but could potentially act through mechanisms relating to its fibre and polyphenol content and associated effects on gut microbiota [407]. At present however, there remains insufficient evidence that dietary patterns independently affect the rate of glycaemic deterioration in early T2DM.

Addressing factors already found to be associated with higher rates of T2DM progression, specifically factors modifiable through lifestyle, such as adiposity and dyslipidaemia [91, 118], should remain the primary targets of dietary intervention in long-term T2DM management. Weight loss as little as 2-5% of bodyweight has been shown to benefit both glycaemia and lipidaemia in people with T2DM [67], with metabolic benefits increasing proportionally with the degree of weight lost. This was demonstrated well in The Diabetes Remission Clinical Trial (DiRECT), whereby significant weight loss induced by very-low energy diets led to remission of T2DM in 86%, 57% and 34% participants for weight losses >15 kg, 10-15kg and 5-10kg respectively during early disease (< 6 years duration) [70, 71]. In later disease, metabolic improvements following weight loss are still observed, albeit to a lesser degree considering much beta-cell dysfunction has become permanent [67, 72]. However, weight re-gain after initial weight loss is common [389, 390] leading to a loss of such metabolic improvements, regardless of T2DM duration [71]. Further research is necessary for how best to prevent weight re-gain longer-term for those with or without T2DM [400].

Participants of Early-ACTID were early in the T2DM disease course, having been diagnosed in the preceding 5-8 months, and were therefore unlikely to have crossed a “point of no return” from which lifestyle modification had reduced effects on HbA1c trajectories; as observed in later disease stages following dramatic weight loss [55], as mentioned above. One possible explanation for the lack of association observed in the current study, if it indeed exists, is potentially insufficient total variation in dietary pattern score change across 1-6 years from which to observe association with changes in HbA1c. Average ‘carb/fat balance’ dietary pattern scores increased only slightly between 0 and 6 months, representing a general improvement in overall diet quality during the first half of the Early-ACTID intervention, but reverted back towards baseline between 6- and 12-months and remaining generally similar across 1-6 years. In much the same way that appropriate interventions

are needed for aiding maintenance of weight-loss, interventions are also needed that can maximise and maintain dietary pattern change long-term in people with T2DM.

This study has many strengths. Firstly, it models glucose-lowering medication-adjusted HbA1c trajectories as a continuous function that changes over time, deriving 'coefficients of failure' for the rate at which HbA1c deteriorates under real-world conditions. Typically, studies that have explored glycaemic deterioration in T2DM have used a dichotomous outcome variable determined by rigid criteria relating to escalating medication use [91]. The 'coefficient of failure' approach avoids rigidly categorising individuals into 'progressor' and 'non-progressor', thus capturing varying degrees of progression and avoids mis-categorisation of individuals due to factors such as, for example, clinical inertia [104]. Secondly, the current study appears to be the first to assess the association of dietary patterns derived using reduced-rank regression on long-term glycaemic deterioration in T2DM. This method for deriving dietary patterns is designed to explain maximal variation in multiple potentially disease-relevant intermediate nutrient intakes, translating these theoretical mechanisms into key food intakes. Insight into mechanisms of action (or inaction) between diet and disease can therefore be clarified, offering a clear advantage over other commonly-used data-driven methods such as principal component analysis (section 2.6.1.2.1). Third, diets were assessed at multiple timepoints over a six year period, allowing greater detail for investigating potential diet-HbA1c outcomes over the long-term. Fourth, as highlighted in many of the preceding chapters, diets were measured using four day food diaries; a measure less affected by reporting bias compared to other self-report measures [139, 140].

Limitations of this study must also be stated. First, there was reduced availability of dietary data at follow-up timepoints 3- and 6-years compared to the first 12-months of the trial. This would have reduced power with which to find evidence of association, should there have been any, between dietary pattern trajectories and HbA1c deterioration during 1-6 years. The poor dietary pattern congruence between baseline and the 3-year timepoint is also a potential result of the reduced sample size at 3-years. Results presented in study 2 (section 4.3.4) showed that repeating RRR at each timepoint independently in only those participants with dietary data available at 3 years (N=127), changed congruence of dietary patterns between baseline and 1-year and 6-years from 'fair' (CC=0.90) to 'poor' (CC<0.85) (Table S8.19). Group-level dietary pattern stability thus appeared lower simply by investigating a smaller sample. Dietary measures for interim follow-up timepoints (two-, four- and five-years after baseline) were also unavailable for analysis. There is also potential bias in effect estimates related to sampling variability in the number of dietary measures available over time, primarily in the disaggregated dietary pattern scores [408]. That is, person-mean dietary

pattern scores (highlighting mean between-person pattern score differences) were calculated from any available diet data; this ranged from 1-5 total measures per participant (median (Q1, Q3): 3 (2, 5)). Variability in the number of measures for each person has been shown to potentially bias between-person effect estimates downwards as a function of the ICC (greater bias the lower the ICC with dietary pattern ICC calculated to be moderate at 0.43) and lower average number of repeat measurements per person ($\bar{n}$<10) [408]. Secondly, as mentioned previously in Chapter 3 and Chapter 4, there is the potential for selection bias due to slight differences between the sample available for analysis and all ACTID participants at baseline. Participants in the analysis sample were slightly older, had lower bodyweight, BMI, beta-cell function and insulin resistance at baseline compared to Early-ACTID as a whole. Crucially, participants willing to join the Early-ACTID trial and engage in long-term follow-up may have been individuals more motivated to manage their T2DM well compared to a typical population of people with T2DM. Third, as is common with all observational analyses, residual confounding of relationships between diet and HbA1c by unmeasured confounders cannot be ruled out. Finally, due to demographic characteristics of the analysis sample, results are mainly generalisable to a white population.

5.5 Conclusion

Adherence to a 'carb/fat balance' dietary pattern did not associate with the rate of glycaemic deterioration in early T2DM. Achieving and maintain weight loss should remain a primary focus for delaying or preventing glycaemic progression.

5.6 Implications for thesis

Study 3 aimed to explore whether a person's dietary pattern associated with the rate at which their glycaemic control deteriorates over the long-term. Study 1 identified associations between a 'carb/fat balance dietary pattern and short-term changes in glycaemic control during the first 6 months of the Early-ACTID trial that were independent of weight changes. Study 3 has extended these analyses by exploring relationships between this dietary pattern and the rate of long-term glycaemic deterioration observed 1-6 years post-trial. However, findings indicate that a person's dietary pattern plays no role in the rate of glycaemic deterioration over time in early T2DM, before

or after accounting for weight change. To check results from study 3 are replicable and generalisable between different cohorts, methods adopted in study 3 will now be repeated in study 4 which analyses a larger, purely observational dataset of people recently-diagnosed with T2DM from across Northern Europe.

Chapter 6 - Study 4: Dietary patterns and glycaemic deterioration in participants of the Diabetes Research on Patient Stratification 2.2 (DIRECT 2.2) observational study

6.1 Introduction

Chapter 5 explored associations between the data-driven, 'carb/fat balance' dietary pattern and long-term rates of glycaemic deterioration in participants who had taken part in the Early-ACTID trial. Results indicated that there was no association between differences in a 'carb/fat balance' dietary pattern and the rate of glycaemic deterioration observed over 1-6 years of trial follow-up. The following study aims to check these findings by repeating analyses in a separate sample of people recently-diagnosed with type 2 diabetes (T2DM); namely, participants of the Diabetes Research on Patient Stratification (DIRECT) 2.2 observational cohort study [404]. Much of the background information presented within the introduction to study 3 (section 5.1) applies equally to the following chapter and is therefore not repeated here.

Key differences between the Early-ACTID and DIRECT 2.2 studies are presented in Table 6.1. DIRECT 2.2 was a 36-month (3-year), purely observational study of people recently-diagnosed (6-24 months) with T2DM residing in England, Scotland, Netherlands, Denmark or Sweden (characteristics described in more detail in sections 6.2.1, 6.2.2 and 6.2.5). DIRECT 2.2 was therefore of shorter total duration compared to the Early-ACTID follow-up (3 vs 5 years) but included a more diverse sample of people with slightly longer disease duration. One potential reason analyses of Early-ACTID data failed to demonstrate evidence of association between dietary patterns and rates of glycaemic deterioration was perhaps a result of limited variability in dietary pattern scores. DIRECT 2.2 participants are more geographically diverse and may thus exhibit greater dietary pattern variation [409]. A potential limitation of DIRECT 2.2 data however, is that dietary intakes were assessed over time using 24-hr records, rather than the 4-day food diaries used in Early-ACTID and its follow-up. Shorter periods of diet measurement may be less able to capture an individual's usual dietary intake [410] and this will need some exploration first. The sample size is however greater within DIRECT 2.2 (a potential N=789 in DIRECT 2.2 vs N=352 analysed in Early-ACTID), increasing power of analysis for detecting potential association. Glutamic Acid Decarboxylase (GAD) antibodies and Islet Antigen-2

(IA-2) antibodies (section 2.4) were also screened for in DIRECT 2.2 but were not in Early-ACTID. Participants potentially misdiagnosed as having type 2 rather than other forms of diabetes, in turn potentially affecting their rate of glycaemic deterioration over time, can thus be explicitly removed from analyses in DIRECT 2.2.

A key difference between datasets was that participants of Early-ACTID received a 12-month intensive lifestyle intervention whereas participants of DIRECT 2.2 did not. An early lifestyle intervention has the potential to affect observed rates of 'real-world' glycaemic deterioration during subsequent follow-up. Derived rates of glycaemic deterioration in the 1-6 year follow-up period of Early-ACTID were however found to be similar to rates observed in purely observational research of Scottish medical records by Donnelly et al [18] (see section 5.4), suggesting that any effect of the Early-ACTID intervention on subsequent HbA1c trajectories were likely only mild. Glycaemic deterioration observed in DIRECT 2.2 would however, not be affected by such issues.

As described in section 5.1, glycaemic deterioration has been modelled previously in DIRECT 2.2 [118]. Bizzotto et al [118] used a conditional linear mixed model [411] to derive medication- and BMI-adjusted HbA1c progression rates for each participant (mean [95%CI]: 0.69 [0.45, 0.93] mmol/mol (0.06 [0.04, 0.09] %) per year). These model-derived progression rates for each participant were then used as outcomes in a second, stepwise multivariable regression model to explore association with potential predictors. This was thus a two-step modelling approach whereby derived rates of glycaemic deterioration in step 1 were treated as true outcomes for each participant for analysis in step 2. This two-step, 'slopes-as-outcomes' method ignores the unexplained variability that exists around the regression line/derived progression rate parameters within the first model and instead treats its beta estimates as perfectly reliable outcomes for use in step 2 [381]. The progression rate parameters derived from the first model are, however, predictions only and their variability when seeking to explore potential associations with other variables can, and should, be accounted for within the same model.

Bizzotto et al [118] assessed only baseline diet for association with the derived progression rate parameters and found no association with either individual nutrient intakes or *a priori* diet index scores that reflected adherence to general 'healthy eating' nutrient, fruit/vegetable and fish intake recommendations [303]. As mentioned in sections 5.1 and 5.4 of Chapter 5, although labelled as a 'dietary pattern' by Bizzotto et al, the diet index scores created from baseline data in DIRECT 2.2 are not truly representative of such as they fail to incorporate any information on how typical food and nutrient intakes combine and correlate with one another. Whether dietary patterns (that is, the

specific combination of foods and nutrients in the diet) associate with glycaemic deterioration in participants of DIRECT 2.2 is therefore yet to be studied. Additionally, diet was assessed at multiple timepoints within DIRECT 2.2 (section 6.2.2) but only data at baseline was included in their analysis.

In the following study, a nutrient-mediated, data-driven dietary pattern, incorporating all available diet data over time, will be explored for potential association with glycaemic deterioration in participants of the DIRECT 2.2 study. Methods used for examining follow-up data from the Early-ACTID trial, presented in Chapter 5, will be replicated as closely as possible to allow maximum scope for comparing results between chapters. Dietary patterns will therefore be derived using reduced-rank regression (RRR) using the same nutrient intermediates used for deriving the 'carb/fat balance' dietary pattern in Early-ACTID; starches and sugars combined, fibre, saturated fat (SFA), monounsaturated fat (MUFA) and polyunsaturated fat (PUFA), which will also allow assessment of the stability of this RRR dietary pattern amongst different populations with T2DM.

Table 6.1: Key differences in study eligibility and measures for Early-ACTID and DIRECT 2.2.

	Early-ACTID	**DIRECT 2.2**
Study type	Multi-centred parallel RCT	Multi-centred observational cohort
Study length	12-month intervention. 5-year follow-up.	3-year follow-up
Study start (year)	2005	2012
Geographical region (N)	South-West England (N=593)	Exeter, Newcastle, Dundee, Amsterdam, Copenhagen, Lund (N=789)
Age eligibility (years)	30-80	35-75
Time since diagnosis eligibility	5-8 months	6-24 months
HbA1c eligibility	Inclusion: <86 mmol/mol (<10%) Exclusion: taking a sulphonylurea medication at the maximum dose	Inclusion: <60 mmol/mol (<7.6%) with or without metformin monotherapy Exclusion: a previous HbA1c >75 (mmol/mol (>9.0%) and prior treatment with non-metformin glucose-lowering medications
GAD and IA-2 assessed?	No	Yes
Lifestyle intervention?	Yes. Intensive dietary advice or Intensive dietary and physical activity advice	No
Dietary measure	4-day food diary	24-hour diet record
Physical activity measure	Waist-worn GT1M uni-axial accelerometer worn over 7 days. Data presented as total proprietary counts per minute.	Non-dominant wrist-worn GT3X+/GT3X+w/GT3X+bt tri-axial accelerometer worn over 10 days. Data presented as average activity intensity at a given time (high-pass-filtered vector magnitude; hpfVM).

GAD – Glutamic Acid Decarboxylase antibodies; IA-2 – Islet Antigen 2 antibodies.

6.2 Methods

6.2.1 Sample

Data came from participants of the Innovative Medicines Initiative (IMI) Diabetes Research on Patient Stratification Study 2.2 (DIRECT 2.2) (Clinical Trial Registration: NCT03814915). Descriptive characteristics of this cohort have been reported in further detail elsewhere [404], but are described briefly here. DIRECT 2.2 was a 3-year, multi-centre prospective cohort study involving 789 white-European adults aged 35-75 and diagnosed with T2DM in the preceding 6-24 months. Its aims (ongoing) are to identify and validate biomarkers related to glycaemic deterioration and disease progression in T2DM [404, 412]. Participants were recruited from local general practices and registries in Exeter, Newcastle, Dundee (UK), Amsterdam (Netherlands), Copenhagen (Denmark) and Lund (Sweden) between November 2012 and September 2014. Management of glycaemia was continued as normal throughout the study according to local therapeutic guidelines for usual care. Participants with Glutamic Acid Decarboxylase (GAD) antibodies ≥11 units/mL or Islet Antigen-2 (IA-2) antibodies ≥7.5 units/mL (n=18) were excluded from analyses to rule out other forms of diabetes [118]. All participants provided written informed consent and the study protocol was approved by regional research ethics review boards.

6.2.2 Dietary data

Diet was self-reported using single 24-hr records the day before each study visit at 0-, 18- and 36-months. All foods and drinks were recorded at the time of consumption, noting cooking methods used and brand names where applicable. Portion sizes were recorded in typical household measures or taken from packet labels. Diet records were coded (externally) by multiple researchers and quality-checked by study dietitians/nutritionists according to a standardised protocol described previously by Gibson et al [334]. This protocol was based on the International Collaborative of Macronutrients, Micronutrients and Blood Pressure (INTERMAP) study [330] and typical portion sizes published by the UK Food Standards Agency [413]. DietPlan (v7; Forestfield Software Limited, UK) was used for analysing all diet data using nutrient data published in the 2015 UK Composition of Foods Integrated Dataset (COFID) [337].

Percentages of total energy intake (TEI) were calculated from dietary intakes using updated Atwater factors [338] for starches and sugars combined, SFA, MUFA, and PUFA using: 100*energy from

nutrient (kJ)/total energy (kJ) at each timepoint. Fibre-density at each timepoint was calculated using total fibre (g)/total energy (MJ). Food items were allocated to 65 groups as defined previously in the derivation of a 'carb/fat balance' dietary pattern in Early-ACTID (Table S8.1). Intakes of each food group were calculated in g/day at 0-, 18- and 36-months for each participant.

6.2.2.1 Preliminary dietary pattern derivation: methods and results

Dietary patterns were derived independently at 0-, 18- and 36-months using reduced-rank regression (RRR), with fibre-density (g/MJ) and percentage energy from starches and sugars, SFA, MUFA, and PUFA (%TEI) used as intermediate variables, repeating methods used in analysis of Early-ACTID dietary data (see section 3.3.4). RRR produces as many dietary patterns as intermediate variables used, and therefore 5 dietary patterns were derived at each timepoint. To identify a single score for each pattern that captured the combination of food groups explaining most variation in the specified nutrient intermediates, only the first pattern was retained for further analysis (Table S8.29).

To confirm whether the dietary pattern structure changed over time, the first patterns derived independently at 18- and 36-months were compared with the first pattern derived at baseline using Tucker's congruence coefficient (CC) [342]. As in previous chapters, a CC>0.85 was taken to indicate dietary patterns were sufficiently similar and suitable for modelling change in a single pattern score over time. However, congruence between dietary patterns derived independently at 0-months (n=688), 18-months (n=491) and 36-months (n=404) was poor (CC<0.85) (Table S8.30), indicating that group-level dietary patterns at each timepoint were not structurally similar to one another (i.e. the size or direction of food group loadings for pattern scores differed significantly across timepoints). To assess whether the poor congruence between timepoints was due to missing diet data, the RRR procedure was repeated at each timepoint independently within complete cases only (n=333). However, dietary pattern congruence between timepoints remained poor (CC<0.85) (Table S8.31).

To test the assumption that a single 24-hr dietary measure was failing to capture participant's usual dietary intakes at each individual timepoint within DIRECT 2.2, a 'carb/fat balance' dietary pattern was derived in data from participants of the Early-ACTID trial, as described in section 5.2.3, but using only a single 24-hrs dietary data at each timepoint (0-, 6-months, 1-, 3- and 6-years) instead of the available four-days. The first dietary patterns derived at baseline and later timepoints in Early-ACTID

were then assessed for structural similarity using Tucker's congruence coefficient [342]. Pattern congruence was then compared between patterns derived using 24-hrs of diet data versus patterns derived using the full four-days of diet data. Results indicated that congruence between dietary patterns derived at each timepoint in Early-ACTID participants dropped from fair (CC>0.85) when using four-days of diet data to poor (CC<0.85) when using only 24-hrs of diet data (Table S8.32).

Based on these preliminary findings, a sample-specific RRR dietary pattern derived using 24-hrs of diet data in participants of DIRECT 2.2 was not considered informative for investigating dietary change, and hence HbA1c change, over time.

6.2.3 Derivation of dietary patterns used in main analyses

As diet data within DIRECT 2.2 was considered unreliable for deriving habitual dietary pattern scores at each individual timepoint, food and nutrient intakes were averaged across 0-, 18- and 36-months. This aimed to provide a better estimate of true, habitual dietary intakes for participants in DIRECT 2.2, reducing potential measurement error that would be magnified by modelling intakes at each timepoint separately. The averaged food and nutrient intakes for each participant were then scored for adherence to the 'carb/fat balance' dietary pattern derived previously in participants of the Early-ACTID trial (Chapter 3). A time-invariant 'carb/fat balance' dietary pattern score was thus created for each participant and used as the primary exposure in all subsequent analyses. The externally-derived 'carb/fat balance' dietary pattern was considered a more reliable dietary pattern to analyse in this population as it was originally derived from four-day food diary data and was found to be structurally stable across time (see sections 5.3.3 and 5.4). Using the same dietary pattern to analyse both the Early-ACTID and DIRECT 2.2 cohorts also allows for greater comparability between study results. As in Early-ACTID, higher 'carb/fat balance' dietary pattern scores remain associated with greater consumption of fresh fruit, low-fat milk, boiled/baked potatoes, and legumes, and also less consumption of higher-fat processed meats, butter/animal fats, red meat, and low-fibre bread (Figure S8.1).

6.2.4 Misreporting of energy intake

As in previous chapters, dietary misreporting in DIRECT 2.2 was assessed via an individualised method [143] that assessed the ratio of reported average energy intake across 0-, 18- and 36-months to estimated energy requirement, calculated from standard equations using an individual's averaged bodyweight over time [375]. Physical activity level (PAL) categories were assigned based on baseline minutes of moderate-vigorous physical activity (MVPA) [344]. Under energy balance, energy intake would be expected to be equal to estimated energy requirements. A 1-SD cut-off [345] around reported energy intake/estimated energy requirement (rEI/EER) (27% in men and 28% in women in DIRECT 2.2) was used assuming energy balance (rEI/EER=1.0) to allocate misreporting status as plausible (i.e. rEI/EER=0.73 to 1.27 for men), under- (i.e. rEI/EER<0.73) or over-reporting (i.e. rEI/EER>1.27). Few over-reporters were identified (n=15) and were therefore combined with plausible-reporters, creating a binary categorical variable (under-reporter and plausible-reporter) for use in subsequent analyses.

6.2.5 Other measures and covariates

Anthropometry, medications, clinical and haematological measures including HbA1c were assessed at five timepoints (0-, 9-, 18-, 27- and 36-months). HbA1c was measured by ion-exchange high-performance liquid chromatography (HPLC) in a single laboratory. Insulin and oral hypoglycaemic agents (OHAs), namely metformin, sulphonylureas, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 agonists were recorded by trained nurses or research assistants as type and dose. To maximise the statistical power of the analyses when adjusting for multiple glucose-lowering medications (Table S8.33), and to replicate methods used in Chapter 5 and by Bizzotto et al. [118], non-metformin/insulin medications (sulphonylureas, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 agonists) were combined into a single variable as a sum of their percentage of maximum doses (range 0-400%) (Table S8.22). Insulin use was treated as a dichotomous variable. Updated homeostasis model assessment of beta-cell function (HOMA2-%B) and insulin resistance (HOMA2-IR) were calculated using standard equations from fasting glucose and fasting endogenous insulin concentrations [109]. Physical activity was assessed over 10 days via non-dominant wrist-worn tri-axial accelerometers (*Actigraph GT3X+; Actigraph LLC, Pensacola, FL, USA*), with data processing described elsewhere [412]. Physical activity estimates were available at baseline only as averaged physical activity intensity at any given time (average high-pass-filtered vector magnitudes (hpfVMs)); an approximation of number of accelerations due to movement in milli-gravities (m*g)*, where *g* is the

magnitude of acceleration due to gravity. Average daily time spent in each category of activity intensity were calculated using established hpfVM cut-offs: sedentary (<139 mg hpfVM), light (139-256 mg hpfVM), and moderate-to-vigorous (>256 mg hpfVM) [414, 415]. Covariates used for analyses were baseline age, sex and smoking status, average TEI, energy under-reporting status and timepoint-specific bodyweight, insulin use and percentage of maximum dose of 1) metformin and 2) non-metformin/insulin glucose-lowering medications.

6.2.6 Statistical analysis

Variables were described using the mean (SD) if approximately symmetric or median (quartile 1, quartile 3) otherwise. To observe how the applied 'carb/fat balance' dietary pattern scores correlated with intermediate nutrient intakes within DIRECT 2.2, Pearson coefficients were calculated between dietary pattern scores and each intermediate nutrient. To help understand what a 1-SD difference in the 'carb/fat balance' dietary pattern score means within DIRECT 2.2, nutrient intake changes relating to a 1-SD increase in dietary pattern score were calculated using simple linear regression, with dietary pattern score as predictor and either fibre-density or percentage energy from starches and sugars combined, SFA, MUFA or PUFA as outcomes. Associations between participant characteristics and 'carb/fat balance' dietary pattern scores in DIRECT 2.2 were explored by describing the sample by quintile of mean dietary pattern score.

Random slope multilevel models with repeated measurements (level 1) nested within participants (level 2) were used to examine HbA1c (outcome) trajectories over time, replicating modelling approaches used in Chapter 5). HbA1c trajectories were modelled linearly in line with evidence indicating glycaemic progression in T2DM is linear over time [18, 92, 101]. Measurement times were modelled as continuous to account for measurement time variation during each measurement wave (Table S8.34) and to avoid information loss. To ensure medications had time to act on HbA1c concentrations, only medications initiated >30 days prior to HbA1c measurements were adjusted for at each measurement wave [118].

A series of multilevel models were used to assess whether dietary pattern scores associated with rates of HbA1c change over time, in line with general analysis structures used in Chapter 3 and Chapter 5: *Model 1* estimated the associations between dietary pattern score interactions with time (exposure) and glucose-lowering medication-adjusted HbA1c (outcome). Predictors in *Model 1* were time, average dietary pattern score and its interaction with time, and disaggregated between/within person glucose-lowering medications and their interactions with time (see Information S8.8). The

interaction between dietary pattern score and time produced a single beta estimate of interest in each model. *Model 2* estimated associations between HbA1c and the dietary pattern and time interaction independent of potential confounders by adding to *Model 1:* baseline age, sex, smoking status, average physical activity intensity and energy under-reporting status, and each of their interactions with time. *Model 3* estimated potential mediation by adding average energy intake and disaggregated between- and within-person bodyweight, and each of their interactions with time to *Model 2*. Units of dietary pattern by time interaction effect estimates within all models were for a 1-SD increase in average dietary pattern score on HbA1c (mmol/mol) per year. Dietary pattern scores in models 1-3 did not require disaggregating into between- and within-person components (as performed in study 3 (Chapter 5)) as the scores in this study were made time-invariant and thus represented only between-person differences in diet. To assess overall change in medication-adjusted HbA1c and hence glycaemic progression from 0-36 months, *Model 1* was repeated without including adjustment for dietary pattern scores and their interactions with time. All models were run using maximum-likelihood estimation. Further specifics of modelling decisions are provided in Information S8.9.

To assess validity of results from *Model 3*, graphical diagnostics were performed to assess assumptions of residual normality and homoscedasticity (over time and over predicted values for HbA1c). Evidence of association was considered when $p<0.05$ for the dietary pattern by time interaction terms and the strength of evidence was assessed by interpreting the clinical relevance of their β and 95%CI. Finally, to aid interpretation of results presented in Chapter 5 and Chapter 6, characteristics of participants included in models 1a-3 in both DIRECT 2.2 and Early-ACTID were tabulated and compared descriptively.

6.2.7 Sensitivity Analyses

The 'carb/fat balance' dietary pattern was originally derived in adults from the South-West of England participating in the Early-ACTID trial (Study 1), and as described in section 6.2.3, was used to score average dietary intakes of participants of DIRECT 2.2. However, participants in DIRECT 2.2 were more geographically diverse than those of the Early-ACTID study, and thus this specific dietary pattern may have captured less dietary intake variation in participants from outside the UK. To assess whether the 'carb/fat balance' dietary pattern did capture intakes similarly across countries within DIRECT 2.2, structural similarity was assessed between the 'carb/fat balance' dietary pattern

derived from baseline in Early-ACTID with the first dietary patterns derived independently at DIRECT 2.2 baseline, in UK participants only and non-UK participants only, using Tucker's congruence coefficient [342]. To also assess how well the 'carb/fat balance' dietary pattern captured variation in mean dietary intakes for all DIRECT 2.2 participants combined, congruence was calculated between the 'carb/fat balance' dietary pattern derived in Early-ACTID and the first dietary pattern derived independently from mean dietary intakes in DIRECT 2.2.

Replicating methods used in Chapter 3 and Chapter 5, in *Model 1a*, the impact of having missing covariate data on *Model 1* estimates was explored by repeating *Model 1* in a restricted sample that had complete data on all covariates that were included in models 2-3. The effects of missing data versus confounder adjustment were differentiated by comparing changes in the β and 95% CI in models 1-1a and models 1a-2. To assess the extent of bias in model estimates from missing HbA1c (outcome) data across time, two binary HbA1c missingness pattern indicators were created as described in section 5.2.7 and each assessed for associations with main model exposure (average dietary pattern scores) and outcome (HbA1c at each separate timepoint) using simple logistic regression. To estimate potential selection bias, differences in characteristics were compared between those in our analysis sample and all those who took part in DIRECT 2.2 at baseline.

To explore potential differences in average dietary intakes between participants who returned different numbers of 24-hr diet records across the study, dietary intakes were compared between those included in Models 1a-3 (one, two or three measures; N=686), complete cases (three measures; N=307), a random two days of diet (N=433) and a random one day of diet (N=686). To assess the effects of having complete dietary data from which to calculate average dietary intakes and hence dietary pattern scores, Models 1a-3 were repeated in those with complete diet data and estimates compared to main model results. Finally, to assess the degree of potential clustering of outcome (HbA1c) variation by geographical location, intra-class correlations (ICC) were calculated from an empty means, three-level random intercept model with HbA1c as outcome (level-1) nested within participants (level-2) nested within research centres (level-3), and Models 1a-3 then compared with and without research centre included at level-3.

Analyses were performed in Stata (v12; StataCorp LLC, College Station, TX, USA), with the RRR procedure incorporating SAS (v9; SAS Institute, North Carolina, USA) (see Information S8.3).

6.3 Results

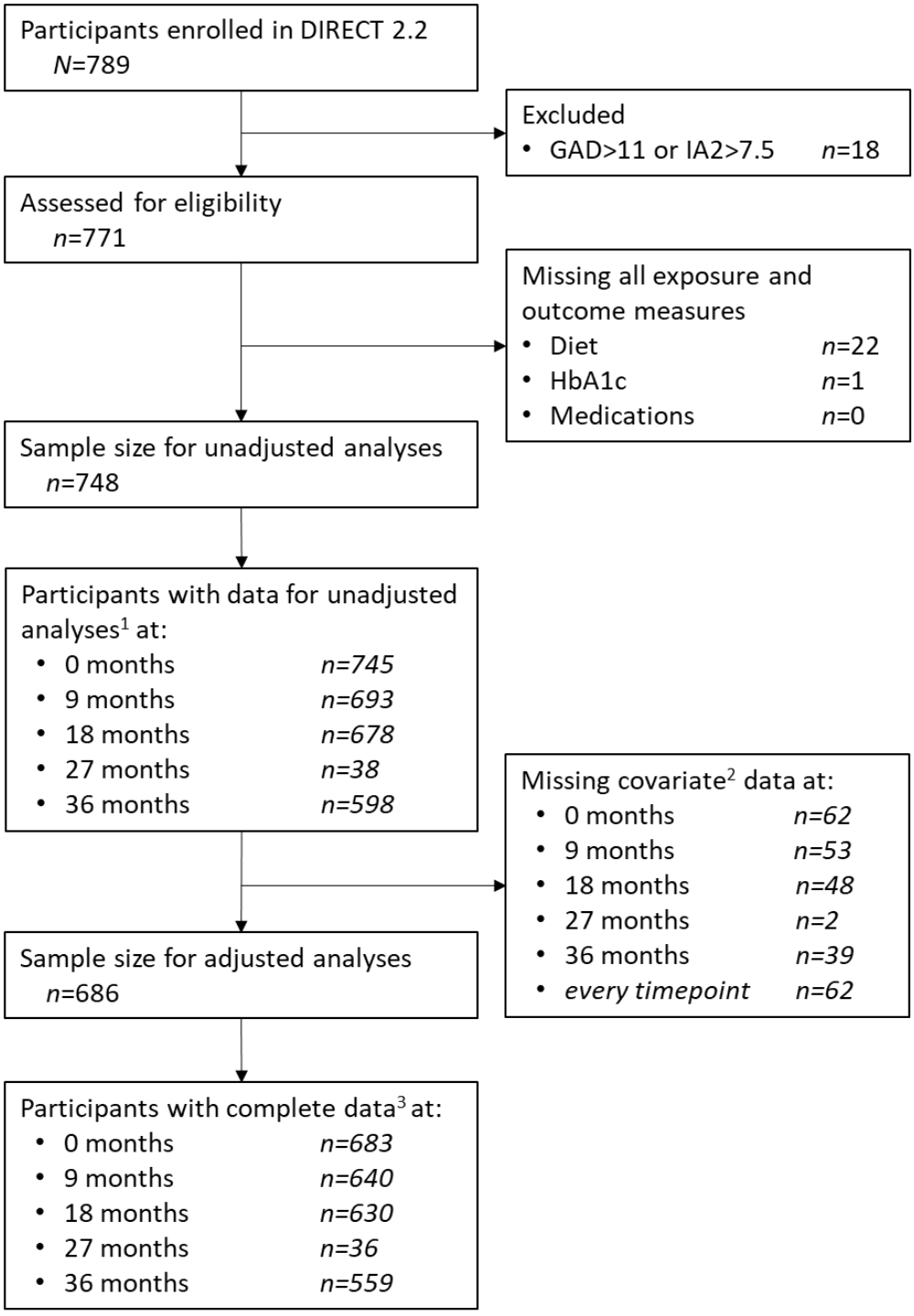
6.3.1 Sample characteristics

Data for adjusted models 1a-3 were available in n=686 participants (92% of those eligible at baseline) (Figure 6.1). At each individual timepoint, complete data was available for n=683, n=640, n=630, n=36 and n=559 participants at 0-, 9-, 18-, 27- and 36-months respectively (Figure 6.1), with a median (quartile 1, quartile 3) number of datapoints per person across the study of 4 (3, 4). Participants with a complete set of data available at baseline (n=683) were more likely to be male (59%) with median age 63 years, weight 88.2kg, BMI 29.8kg/m^2, HbA1c 46 mmol/mol (6.4%), with 34% taking metformin (Table 6.2). Participants with data available for inclusion in models 1a-3 at 36 months compared to participants included in models 1a-3 at baseline were slightly older at baseline (median 64 vs 63 years), with relatively less participants from Exeter (10% vs 16%) and relatively more from Dundee (28% vs 23%), but were otherwise similar (Table 6.2). Raw HbA1c concentrations remained similar from 0-36 months but the number of participants requiring glucose-lowering medications increased (34% to 46% on metformin; 0% to 7% on non-metformin/non-insulin medications; 0% to 1% on insulin) (Table 6.2).

Average dietary intakes for those in models 1a-3 are presented in Table 6.3. Higher 'carb/fat balance' dietary pattern scores again correlated with higher percentage energy from starches and sugars (r=0.68) and fibre-density (r=0.49), and lower percentage energy from SFA (r=-0.55), MUFA (r=-0.56) and PUFA (r=-0.21). A 1-SD higher 'carb/fat balance' dietary pattern score equated to consuming 5.0% more energy from carbohydrate (4.8% from combined starches and sugars and 0.3g/MJ more fibre) and -3.7% less energy from fat (-1.7%, -1.6%, -0.4% from SFA, MUFA, and PUFA respectively). At baseline, participants who had higher average carb/fat balance dietary pattern scores (Table S8.35 quintile 5) were more likely to be female, have lower energy intake but also more likely to under-report energy intake, had higher baseline bodyweight and beta-cell function, had slightly lower disease duration and were less likely to be on metformin medication.

Compared to all DIRECT 2.2 participants, the analysis sample contained slightly more men (57% vs 59%) but was otherwise similar (Table S8.36).

Figure 6.1: Sample size flow chart.



[1] Participant data that is complete at a given timepoint is retained within a multilevel model. Any missing data in either predictor, outcome or covariate at a given timepoint will lead to removal of all data for that individual at that specific timepoint only. Data is therefore not required to be balanced over time. [2] baseline age, sex, smoking status, mean physical activity intensity, energy misreporting status, timepoint-specific bodyweight and energy intake. [3] complete data for mean dietary pattern score, mean energy intake, baseline age, sex, smoking status, mean physical activity intensity, energy misreporting status, and timepoint-specific HbA1c, glucose-lowering medications and bodyweight. GAD – Glutamic Acid Decarboxylase antibodies (units/mL); IA-2 – Islet Antigen-2 antibodies (units/mL).

Table 6.2: Characteristics of participants included in Models 1a-3 (N=686) at each timepoint.

	0 months	9 months	18 months	27 months	36 months
n (% of N=686)	683 (99.6%)	640 (93%)	630 (92%)	36 (5%)	559 (81%)
Research centre					
Exeter, England	107 (16%)	96 (15%)	79 (13%)	0 (0%)	56 (10%)
Newcastle, England	159 (23%)	154 (24%)	156 (25%)	0 (0%)	141 (25%)
Dundee, Scotland	160 (23%)	152 (24%)	157 (25%)	3 (8%)	154 (28%)
Amsterdam, Netherlands	137 (20%)	127 (20%)	117 (19%)	0 (0%)	101 (18%)
Copenhagen, Denmark	35 (5%)	37 (6%)	38 (6%)	33 (92%)	28 (5%)
Lund, Sweden	85 (12%)	74 (12%)	83 (13%)	0 (0%)	79 (14%)
Male	406 (59%)	379 (59%)	375 (60%)	23 (64%)	330 (59%)
Baseline age (years)	63 (57, 68)	64 (58, 68)	64 (58, 68)	64 (58, 69)	64 (57, 68)
Baseline disease duration (years)	1.0 (0.5, 1.6)	1.0 (0.5, 1.6)	1.0 (0.5, 1.6)	1.1 (0.4, 1.8)	1.0 (0.5, 1.5)
Baseline smoker	97 (14%)	79 (12%)	82 (13%)	6 (17%)	72 (13%)
Baseline mean physical activity intensity (hfvpm; mg)	34 (28, 40)	34 (28, 40)	34 (28, 40)	33 (28, 38)	34 (28, 40)
Baseline MVPA (mins/day)	41 (30, 53)	41 (31, 53)	41 (30, 54)	35 (31, 47)	42 (31, 55)
Weight (kg)	88.2 (76.8, 100.8)	87.8 (77.1, 101.0)	87.3 (76.6, 100.8)	85.5 (75.7, 101.4)	86.7 (77.3, 100.5)
BMI (kg/m2)	29.8 (26.7, 33.7)	29.7 (26.8, 33.6)	29.8 (26.6, 33.2)	28.2 (25.5, 31.4)	29.8 (26.9, 33.5)
HbA1c (mmol/mol)	46 (43, 50)	47 (43, 52)	47 (43, 52)	47 (43, 52)	46 (42, 52)
HbA1c (%)	6.4 (6.1, 6.7)	6.5 (6.1, 6.9)	6.5 (6.1, 6.9)	6.4 (6.0, 6.9)	6.4 (6.0, 6.9)
HOMA2-%B	91 (70, 114)	-	84 (67, 108)	-	85 (65, 110)
HOMA2-IR	2.5 (1.9, 3.2)	-	2.7 (2.1, 3.5)	-	2.8 (2.1, 3.7)
On metformin	232 (34%)	236 (37%)	266 (42%)	26 (72%)	259 (46%)
Metformin (%max dose)	0 (0, 17)	0 (0, 33)	0 (0, 33)	33 (4, 67)	0 (0, 33)
On non-metformin/non-insulin medications	0 (0%)	5 (1%)	13 (2%)	1 (3%)	40 (7%)
Non-metformin/non-insulin medications (%max dose)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
On insulin	0 (0%)	2 (0.3%)	4 (1%)	0 (0%)	6 (1%)

Data presented as median (quartile 1, quartile 3) or n(%). *hpfVM – high-pass filter vector magnitude; mg – milli-gravities; MVPA – moderate-to-vigorous physical activity; BMI – body mass index; HOMA2-%B – homeostasis model assessment of beta-cell function; HOMA2-IR – homeostasis model assessment of insulin resistance.*

Table 6.3: Diet characteristics for sample included in models 1a-3 (n=686).

Carb/fat balance dietary pattern score		-0.24 (-0.97, 0.50)
Energy intake (kJ)		7365 (6009, 8861)
Total carbohydrate (%TEI)		45.4 (40.6, 51.3)
Starches and sugars (%TEI)		43.8 (39.0, 49.5)
Fibre (g/MJ)		1.9 (1.5, 2.3)
Protein (%TEI)		18.9 (16.2, 21.8)
Total fat (%TEI)		34.3 (29.3, 39.0)
SFA (%TEI)		12.2 (10.0, 14.8)
MUFA (%TEI)		11.5 (9.4, 13.5)
PUFA (%TEI)		5.3 (4.0, 6.7)
Alcohol (%TEI)		0 (0, 2.5)
Energy under-reporters (n(%))		354 (52%)
Highest positive loading food groups		
Fruit (fresh), g/d		114 (45, 190)
	% consumers	81
Low fat milk, g/d		153 (41, 268)
	% consumers	81
Boiled/baked potatoes, g/d		20 (0, 87)
	% consumers	51
Legumes, g/d		0 (0, 10)
	% consumers	28
Meat substitutes, g/d		0 (0, 0)
	% consumers	2
Highest negative loading food groups		
Higher fat processed meats, g/d		3 (0, 34)
	% consumers	51
Butter & animal fats, g/d		0 (0, 6)
	% consumers	38
Red meat, g/d		0 (0, 33)
	% consumers	34
Low fibre bread, g/d		25 (0, 60)
	% consumers	63
Fried/roast, chips & other potato with added fat, g/d		0 (0, 47)
	% consumers	39

Data presented as median (quartile 1, quartile 3) or n(%). *TEI – total energy intake; SFA - saturated fat; MUFA - monounsaturated fat; PUFA - polyunsaturated fat.*

6.3.2 A 'carb/fat balance' dietary pattern did not associate with deterioration in HbA1c

After adjusting for glucose-lowering medications, HbA1c increased at a rate of 0.60 [95%CI: 0.31, 0.90] mmol/mol (0.05 [0.03, 0.08] %) per year (p<0.001). There was no evidence that a 'carb/fat balance' dietary pattern score associated with the rate of change in HbA1c, before or after adjusting

for potential confounders and mediators (Table 6.4). Model diagnostics revealed no major issues with residual normality or homoscedasticity (Figure S8.14).

Table 6.4: Associations between differences in mean 'carb/fat balance' dietary pattern score and rate of change in HbA1c in the DIRECT 2.2 study.

β's represent the change in HbA1c per year associated with a 1-SD higher mean dietary pattern score over the course of the study.

Model	n	β	95%CI	p
1	748	-0.06	-0.25, 0.14	0.572
1a	686	0.01	-0.19, 0.20	0.957
2	686	0.02	-0.18, 0.22	0.844
3	686	-0.03	-0.23, 0.17	0.763

1 – Random linear slope multilevel model for HbA1c (outcome) adjusted for continuous time, dietary pattern score and its interaction with time, disaggregated between- and within-person glucose-lowering medication (namely metformin, non-metformin/insulin and insulin) doses and their interactions with time.

1a – Model 1 restricted to sample with complete sets of covariate data for at least one timepoint.

2 – Model 1a adjusted for baseline sex, age, smoking status, mean physical activity intensity and energy under-reporting status (potential confounders) and their interactions with time.

3 – Model 2 adjusted for mean energy intake and disaggregated between- and within-person bodyweight (potential mediators) and their interactions with time.

6.3.3 Sensitivity analyses

Structural similarity of the 'carb/fat balance' dietary pattern derived from Early-ACTID data at baseline was poor with the first dietary pattern derived independently in UK participants only (CC=|0.83|) and non-UK participants only (CC=|0.37|) at baseline, and from mean intakes in all participant of DIRECT 2.2 combined (CC=|0.71|). CC's thus indicated the greatest divergence was between the Early-ACTID 'carb/fat balance' dietary pattern and RRR dietary patterns derived independently in non-UK participants. There was no evidence of association prior to adjusting for covariates between the 'carb/fat balance' dietary pattern score and rate of change in medication-adjusted HbA1c, before or after restricting the sample to those with complete covariate data (Table 6.4 Models 1-1a). Neither mean dietary pattern score nor HbA1c were found to associate with either HbA1c missingness pattern indicator (Table S8.37 and Table S8.38), indicating missing HbA1c values could be assumed to be missing at random (MAR) and model associations were not confounded by missing outcome data. Average group-level dietary intakes were not found to be significantly

affected by the number of 24-hr diet records returned by participants across timepoints (Table S8.39). Finally, there was no evidence that accounting for potential clustering of HbA1c values by geographical region or restricting models 1-3 to those with complete dietary data at 0-, 18- and 36-months (n=333) affected main results (Table S8.40 and Table S8.41).

6.4 Discussion

This study examined whether a 'carb/fat balance' dietary pattern associated with rates of glycaemic deterioration in participants of the European, multi-centre DIRECT 2.2 cohort study. Average medication-adjusted HbA1c trajectories in DIRECT 2.2 demonstrated mild deterioration over three years (0.60 mmol/mol (0.05%) per year). However, no evidence was found linking rates of glycaemic deterioration in DIRECT 2.2 with overall adherence to a 'carb/fat balance' dietary pattern.

Participant medication-adjusted HbA1c concentrations were found to deteriorate at a rate of 0.60 mmol/mol (0.05%) per year, in line with rates calculated previously in DIRECT 2.2 using alternative modelling strategies (0.69 mmol/mol (0.06%) per year adjusted for BMI using a conditional linear mixed model [411]) [118]. Although known to be highly variable amongst individuals, mean HbA1c deterioration rates in DIRECT 2.2 may therefore be considered somewhat mild compared to rates observed in other recently-diagnosed populations (1.4 mmol/mol (0.13%) per year in observational research of n=5,342 over 9.4 years on combination therapy by Donnelly et al [18], 1.5 mmol/mol (0.14%) per year in n=1,454 participants over 4 years on metformin monotherapy within the ADOPT trial by Kahn et al [17], and 1.49 mmol/mol (0.14%) per year over 5 years on combination therapy following the Early-ACTID trial (Chapter 5)). This is a potential result of strict eligibility criteria for inclusion within DIRECT 2.2: participants were recruited if HbA1c at screening was <60mmol/mol (<7.6%) controlled by either lifestyle or metformin monotherapy only (versus <86 mmol/mol (<10%) at screening controlled by lifestyle, metformin or a sub-maximum sulphonylurea dose in Early-ACTID). Participants of DIRECT 2.2 were also recruited if a T2DM diagnosis had been made within 6-24 months prior (vs 5-8 months prior for Early-ACTID). HOMA2-%B and HOMA2-IR values indicate that participants in DIRECT 2.2 had greater beta-cell secretion levels and lower insulin resistance levels compared to participants in Early-ACTID at baseline (median 91% vs 77% and 2.5 vs 4.6 respectively; data presented together in Table S8.42), suggesting greater residual beta-cell function in the DIRECT 2.2 cohort as a whole. Recruitment of participants in DIRECT 2.2 was therefore biased

towards those with low baseline glycaemia and also slower progression, as those with higher baseline glycaemia, or more rapid progression, were less likely to be recruited.

This study replicated analyses and findings presented in Chapter 5, finding no evidence of association between dietary patterns and glycaemic deterioration in early T2DM. DIRECT 2.2 benefitted from having a larger sample size for analyses in models 1a-3 compared with in Early-ACTID (N=686 vs N=352). Although there was a greater proportion of males in both samples, this was to a lesser degree compared to in the Early-ACTID sample (59% vs 66%; data presented together in Table S8.42). Average age, baseline HbA1c and the proportion of participants on metformin at baseline were similar between studies but the proportion of smokers, duration of disease, bodyweight and minutes of MVPA per day were all greater in DIRECT 2.2 compared with Early-ACTID (14% vs 8%; 1.0 vs 0.5 years; 88.2 vs 86.9kg; 41 vs 21 minutes respectively). Although DIRECT 2.2 participants may have been more active, differences between cohorts in estimated minutes of MVPA each day is contributed to by differences in wear-position of accelerometers (wrist- or waist-worn), data processing procedures and accelerometer metrics used [416].

Participants in Early-ACTID and DIRECT 2.2 had generally similar nutrient intakes at baseline (data re-presented in Table S8.43). 'Carb/fat balance' dietary pattern scores were however slightly lower on average in DIRECT 2.2 (median -0.24 vs 0.04 SD), suggesting lower quality diets overall but only to a slight degree. This appeared to be a result of a greater percentage of participants in Early-ACTID consuming the highest positive loading food groups compared to in DIRECT 2.2 (for example, 93% vs 81% consumed fresh fruit; 69% vs 28% consumed legumes). In turn, median intakes were also higher for highest positive loading food groups in Early-ACTID compared to in DIRECT 2.2 (157 vs 114g/day of fresh fruit; 18 vs 0g/day of legumes). The greater percentage of participants consuming highest negative loading food groups between Early-ACTID and DIRECT 2.2 depended on the food group. In Early-ACTID versus DIRECT 2.2, 57% vs 51% consumed higher-fat processed meats but 49% vs 63% consumed low-fibre bread (median intakes 3 vs 10g/day higher-fat processed meats and 0 vs 25g/day low-fibre bread). Such differences may have been related to fewer days of measurement of dietary intakes in DIRECT 2.2 (1 to 3 measurement days over 0-36 months) compared with Early-ACTID (4 measurement days at baseline), less successfully capturing certain dietary intakes. However, it is also potentially because of the projection of an externally derived, possibly sample-specific 'carb/fat balance' dietary pattern from the Early-ACTID trial onto DIRECT 2.2 dietary data. The 'carb/fat balance' dietary pattern was the weighted linear combination of foods best explaining maximal variation in the intakes of carbohydrate and fat sub-types in participants of Early-ACTID. This dietary pattern was subsequently used to score dietary intakes of participants in DIRECT 2.2,

because deriving a sample-specific pattern from the available data in DIRECT 2.2 was deemed unreliable (see further discussion in study limitations below). The 'carb/fat balance' dietary pattern from Early-ACTID was however found to be incongruent with dietary patterns derived independently in UK participants only, non-UK participants only, or all participants combined in DIRECT 2.2 using the same RRR method as used in Early-ACTID. Additionally, a 1-SD difference in 'carb/fat balance' dietary pattern scores in DIRECT 2.2 equated to slightly less change in total carbohydrate (5.0% vs 7.0% TEI) and total fat intakes (3.7% vs 4.9% TEI) than in diets of Early-ACTID, suggesting this combination of foods captured less variation in intermediate nutrient intake in DIRECT 2.2. However, group-level variation in mean dietary pattern scores was still greater in DIRECT 2.2 compared to at Early-ACTID baseline (median (quartile 1, quartile 3): -0.24 (-0.97, 0.50) SD versus 0.04 (-0.53, 0.49) SD; Table 5.2), likely as a result of greater geographical and hence culinary diversity within DIRECT 2.2 [409]. A lack of evidence for association between dietary pattern scores and rates of glycaemic deterioration in DIRECT 2.2 does not therefore appear solely due to a lack of variation in dietary exposure, even if the 'carb/fat balance' dietary pattern failed to capture maximal variation in recorded nutrient intakes in this dataset.

As in Early-ACTID, participants in DIRECT 2.2 were generally following diets containing moderate carbohydrate (45%TEI) intakes [417]. It is thus not possible to comment on the potential effects of low- (<26%TEI) or very low-carbohydrate (<10%TEI) diets as participants were not generally following them. A removal of carbohydrate from the diet has previously been associated with reduced need for glucose-lowering medications [192, 288], but whether this coincides with prolonged survival of beta-cell function is unknown. Current evidence indicates that without weight loss, underlying beta-cell pathology remains and the inability to manage glycaemia upon any reintroduction of carbohydrates will progress [209]. Delaying or preventing glycaemic progression via diet therefore only appears possible through the weight-reducing effects of lowering overall energy intake, provided this takes place early enough in the disease process [70]. There thus remains little evidence that any specific combination of nutrients and foods in the diet plays a role in preventing or delaying glycaemic deterioration, outside of helping facilitate reductions in energy intake. The focus of long-term dietary management of type 2 diabetes should thus remain centred around promoting and helping maintain weight loss.

This study has many strengths. Firstly, this analysis replicates the null findings obtained in study 3 but in a larger, more diverse sample of people recently-diagnosed with T2DM, with a smaller drop in sample size over time. Combined with the analyses presented in Chapter 5, the current study is one of only two that explore associations between nutrient-mediated, data-driven dietary patterns and

longer-term glycaemic deterioration in T2DM. It demonstrates that diets varying in the amount of total carbohydrate, fat and overall food quality appear to play no independent role in arresting chronic deterioration of glycaemia in early disease; at least under moderate nutrient intake levels. Secondly, HbA1c deterioration has been modelled as continuous rather than, as in the majority of current literature, a dichotomous outcome assessing progression as the time to starting or escalating medications [418]. This allowed for varied degrees of glycaemic progression to be explored for associations with diet, avoiding mis-categorising individuals as 'progressor' or 'non-progressor' due to issues relating to clinical inertia [103] or where there is only partial progression towards failure. Third, analyses have been performed in participants who did not receive an intensive lifestyle intervention such as that received by participants of the Early-ACTID trial, therefore glycaemic deterioration rates were unaffected by any potential ongoing effects of an earlier intervention. Fourth, variation in average dietary pattern scores was greater in DIRECT 2.2 compared to in Early-ACTID, reducing the chances that insufficient dietary pattern variation was a cause of the null findings from study 3.

There are however a number of key limitations of this study which require further discussion. Firstly, the measurement tool used to assess dietary intakes in DIRECT 2.2 was a single 24-hr diet record repeated at 0-, 18- and 36-months. As recognised in the literature, single 24-hr diet records are unlikely to capture usual dietary intakes [410]. Measuring a person's usual dietary intake is needed for assessing individual-level associations between habitual diet and long-term health [419]. When the first pattern derived independently at DIRECT 2.2 baseline was compared with that at 18- and 36-months, group-level dietary patterns were found to be incongruent (structurally dissimilar) over time. This was true even when restricting the sample to complete diet data across the study. As participants of DIRECT 2.2 had received no dietary intervention outside of usual medical care, dietary patterns would not be expected to change to a high degree at group-level as group-level dietary patterns have been demonstrated to typically remain consistent over time [420–424]. Dietary patterns derived from participants of the Early-ACTID study at each timepoint independently, demonstrated greater pattern structural stability over a longer time period (6 years) using 4-day food diaries to measure dietary intakes, and this remained true even in the context of receiving an intensive dietary intervention (Chapters 3-5). However, sensitivity analyses demonstrated that Early-ACTID dietary patterns became incongruent between timepoints when restricting the dietary measures from four-day records to only single-day records for each timepoint, suggesting a shorter-term measure failed to capture group-level dietary patterns appropriately. A sample-specific RRR dietary pattern derived from 24-hr dietary data at each timepoint was therefore not considered to be reliable for modelling dietary intake change over time in DIRECT 2.2. As a pragmatic choice

therefore, dietary intakes were averaged across available timepoints for each participant, under the assumption that this would better capture usual intakes. A limitation of this approach is that episodically-consumed foods may have remained uncaptured at the individual level [425], but more complex statistical methods of calculating usual intakes from short-term measures were deemed impractical for subsequent use in a reduced-rank regression analysis [425–428]. Scoring dietary intakes in DIRECT 2.2 against the more robust 'carb/fat balance' dietary pattern derived from repeated four-day food diaries in the Early-ACTID trial aimed to avoid magnifying measurement error within the 24-hr diet records compared to if attempting to derive a sample-specific, data-driven dietary pattern from DIRECT 2.2 mean dietary data itself. Furthermore, projecting the Early-ACTID dietary pattern structure onto DIRECT 2.2 dietary data enabled results from study 3 and 4 to be more easily comparable, a common problem between studies involving data-driven dietary patterns [167].

A second limitation of the current study is that there was less dietary data available at later timepoints, meaning averaged dietary intakes for some participants were calculated from only one or two measures at 0- or 18-months. This would be of potential concern given that a single measure may be unsuitable for measuring habitual intakes, but sensitivity estimates in models limited to complete dietary data over time reached the same overall conclusions as from the main results. Thirdly, assessment of misreporting status classified 52% of participants as under-reporting energy intake. Although high, it should be noted that a stricter 1-SD cut-off was used for plausible deviation from unity in the ratio of reported energy intake to calculated total energy expenditure, assuming energy balance, compared with a 2-SD (95%CI) deviation used in some studies using similar methods [143, 325, 429]. A 1-SD plausible deviation will thus identify greater numbers of potential energy under-reporters, versus a 2-SD deviation, which can be considered too lenient towards extremely inaccurate dietary data [345, 430]. Nevertheless, main model estimates were not found to be affected by adjustment for under-reporting status. Fourth, diet compositions for participants from Netherlands, Denmark and Sweden were analysed using a UK-specific nutrient composition database, potentially introducing errors into estimated nutrient intakes of non-UK participants in DIRECT 2.2. Fifth, there remains potential, as with all observational studies, for model estimates to be affected by residual confounding. Finally, due to demographic characteristics of the analysis sample, results of this study are mainly generalisable to a white, northern European population.

6.5 Conclusion

Glycaemic deterioration in participants of the DIRECT 2.2 cohort study was not associated with adherence to a 'carb/fat balance' dietary pattern, replicating the null findings observed in similar analyses in participants who had taken part in the Early-ACTID trial. Echoing the conclusions of study 3 therefore, to promote mitigation of glycaemic deterioration, achieving and maintaining weight loss in ways most accessible to each individual should remain the focus of long-term T2DM dietary management.

6.6 Implications for thesis

Findings from study 4 indicated that a dietary pattern balancing carbohydrate and fat intakes did not associate with the rate of glycaemic deterioration in participants of the DIRECT 2.2 observational study, agreeing with the null findings presented in study 3 from a similar analysis of data from Early-ACTID's 5-year follow-up. This thesis has therefore been unable to demonstrate any evidence associating dietary patterns with the rate of glycaemic deteriorations in early T2DM. Balancing carbohydrate and fat intakes around UK healthy eating guidelines may provide small benefits to glycaemic control independent of weight change during the shorter-term for periods up to 6 months, but this does not extend to delaying glycaemic deterioration over the longer-term.

Chapter 7 - Overall Discussion

This final chapter is a summary of the findings of this thesis and considers their implications on current guidelines for managing people with Type 2 diabetes (T2DM). The implications of these findings for future research on the role that diet plays in the progression of T2DM is also discussed.

7.1 Key findings

7.1.1 Study 1

Study 1 sought to answer research question 1: *Do changes in nutrient-mediated dietary patterns associate with short-term glycaemic control independent of the effects of weight change in early type 2 diabetes?* Previous studies exploring the effects of changes in dietary composition on changes in glycaemic control have found conflicting evidence for the most appropriate intakes, potentially as a result of co-occurring weight changes confounding results. In agreement with prior literature and current guidance promoting weight loss in people with T2DM, findings from a secondary analysis of data from the Early-ACTID trial indicated that weight loss was associated with improvements in glycaemic control. Within this analysis, changes in food intakes were scored using two data-driven dietary patterns derived to explain maximal variation in different combinations of nutrient intakes: one combination of nutrients theorised to relate diet with glycaemia directly (labelled a 'carb/fat balance' pattern) and one theorised to relate diet with glycaemia indirectly via bodyweight (labelled an 'obesogenic' pattern). Changes in both dietary patterns associated with changes observed in bodyweight. Furthermore, increases in 'carb/fat balance' dietary pattern scores associated with small benefits to glycaemic control independent of the effects of weight loss. An increase in 'carb/fat balance' dietary pattern score translated to carbohydrate intakes shifting higher and fat intakes shifting lower, balancing total carbohydrate and fat intakes around general UK healthy eating recommendations through greater consumption of fresh fruit, low-fat milk, boiled/baked potatoes and legumes and eating less higher-fat processed meats, butter/animal fats, red meat and low-fibre bread. Thus, although inducing weight loss remains the key mechanism through which diet can improve glycaemic control, small, additional benefits appear to be possible in the short-term through modifying dietary pattern.

7.1.2 Study 2

Study 2 sought to answer research question 2: *During and following a non-prescriptive, patient-centred dietary intervention in early type 2 diabetes, do dietary pattern changes diverge between men and women?* Previous research has indicated that typical dietary behaviours in men and women differ, potentially as a result of differences between them in biology and sociocultural norms. Few studies have looked at typical dietary patterns in people with T2DM and whether these patterns differ between men and women. Importantly, it was not known whether differences in typical dietary behaviours between the sexes might lead to differing dietary pattern responses after receiving non-prescriptive dietary advice. Study 2 therefore aimed to explore this. Trial dietitians in Early-ACTID provided a non-prescriptive, patient-centred dietary intervention to people recently diagnosed with T2DM, mimicking the approach typical of current UK dietetic practice. Findings from study 2 demonstrated that although dietary patterns were likely to be more 'obesogenic' in men compared with women, in agreement with unhealthier food choices attributed to men in the wider literature, dietary pattern changes made during different periods of the Early-ACTID trial, and its 5 years of subsequent follow-up were found to be similar in both sexes. Any differences that may typically exist in dietary behaviours in men and women thus appear to be mitigated under a typical, patient-centred approach. Study 2, therefore, provided no evidence that dietary interventions in early T2DM require further tailoring by sex in order to achieve similar levels of dietary pattern change in both men and women and should instead remain tailored to initial diet quality. However, despite dietetic advice leading to improvements in dietary patterns in both sexes during the first 6 months of Early-ACTID, the overall magnitude of dietary pattern changes were small and were not maintained longer-term in this population.

7.1.3 Study 3

Study 3 sought to answer research question 3: *Do nutrient-mediated dietary patterns associate with longer-term glycaemic progression in early type 2 diabetes?* As there is considerable unexplained heterogeneity in the rate at which T2DM progresses between individuals, study 3 aimed to explore whether the dietary pattern followed by an individual might be a contributing factor. In study 1, a dietary pattern balancing total carbohydrate and fat intakes around UK healthy eating recommendations was found to associate with changes in glycaemic control independent of weight change during the first six months of the Early-ACTID trial. Study 3 extended such analyses by exploring associations between this dietary pattern and glycaemic deterioration observed during 5

years of post-trial follow-up. This study appears to be the first to explore associations between data-driven dietary patterns and the rate of glycaemic deterioration in early T2DM. However, findings indicated that a dietary pattern balancing total carbohydrate and fat intakes plays no role in how glycaemic control deteriorates over time and hence the rate at which T2DM progresses.

7.1.4 Study 4

In addition to answering research question 3, study 4 sought to answer research question 4: *Are associations between nutrient-mediated dietary patterns and longer-term glycaemic progression in early type 2 diabetes replicable and generalisable between cohorts?* Findings from study 3 indicated that a dietary pattern balancing carbohydrate and fat intakes did not associate with the rate of glycaemic deterioration observed during 5 years of follow-up of the Early-ACTID trial. Study 4 sought to repeat these analyses in the DIRECT 2.2 observational study; a larger sample of people recently diagnosed with T2DM, with greater geographical diversity and hence potential for dietary pattern diversity, than in Early-ACTID. However, preliminary analysis of available dietary data in DIRECT 2.2 indicated it was likely not representative of usual dietary intakes in this sample and was thus deemed unreliable for deriving a sample-specific, data-driven dietary pattern for assessing change in diet over time. Therefore, the more reliable 'carb/fat balance' dietary pattern, derived externally within participants of Early-ACTID, was applied to dietary data averaged over time in DIRECT 2.2. This was advantageous in that using the same dietary pattern to score dietary intakes in both study 3 and 4 allowed for easier comparison and assessment of the reliability and generalisability of results between cohorts. Findings from study 4 agreed with those from study 3, finding no association between a time-averaged 'carb/fat balance' dietary pattern and the rate of glycaemic deterioration observed during 3 years of the DIRECT 2.2 study.

7.1.5 Summary of main findings

The research presented within this thesis has been the first to explore changes in nutrient-mediated, data-driven dietary patterns over both the short- and long-term and their associations with glycaemia in early T2DM. It has demonstrated that a dietetic intervention in early T2DM is capable of beneficially changing dietary patterns in line with advice similarly in both men and women, but over the short-term only. How changes in dietary patterns can be maintained longer-term warrants

further investigation as greater or alternative support appears to be necessary. Separately, dietary patterns balancing carbohydrate and fat intakes may benefit glycaemic control in early T2DM over the short-term, independent of any co-occurring weight loss, but this does not extend to impacting how disease progresses over the long-term. Specifically, the rate at which glycaemia deteriorates in early T2DM due to ongoing decline of beta-cell function does not appear to be impacted by the specific combination of foods and nutrients consumed within the diet. Conclusions cannot be generalised to non-white populations and apply primarily to diets containing typically moderate-to-high amounts of carbohydrates (ranging 39-54% total energy) and fats (28-41% total energy) (Table S8.35), with higher-carbohydrate/lower-fat dietary intakes associating with generally higher quality food choices, and vice versa. Findings do not inform on the potential effects of nutrient intakes outside of the ranges stated. Therefore, the effects of dietary patterns containing much lower amounts of carbohydrate or that differentiate carbohydrate and fat quality to a greater degree should be researched further. A factor identified from previous research that has been linked with slower disease progression, and which is indeed modifiable by diet or lifestyle, is a reduction in bodyweight. This should remain the primary focus for long-term dietary management of T2DM and is the overall conclusion of this thesis.

7.2 Implications for the clinical management of type 2 diabetes

Overall, the findings of this thesis fall in line with what is already recommended for dietary management in T2DM. Current National Institute of Health and Care Excellence (NICE) guidelines [431], Diabetes UK nutritional guidelines [20] and American Diabetes Association guidelines [432], amongst others, emphasise an individualised approach to nutrition therapy for adults with T2DM. Interventions are recommended to be tailored to the needs and preferences of the patient, acknowledging that there is no 'one-size-fits-all' approach. Likewise, the Early-ACTID trial used a non-prescriptive, patient-centred approach to promote dietary change in people recently diagnosed with T2DM. Findings from this thesis indicated that dietary patterns can indeed improve in this population following dietitian-led, patient-centred advice, benefitting both men and women equally. Of main concern however, was the poor level of maintenance of these dietary changes observed post 6 months in Early-ACTID and its 5 years follow-up. Poor long-term maintenance of lifestyle change following an intervention has of course been recognised in previous studies and is not a new finding. However, NICE and Diabetes UK recommend structured diabetes education at the time of diagnosis followed by annual reinforcement [20, 431]. Although Early-ACTID participants received

one-to-one rather than more typical group-based advice (the latter being offered to people newly-diagnosed with T2DM in the UK through programmes such as Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) or X-PERT [433, 434]), annual follow-up was not sufficient to maintain dietary pattern changes in either sex. Patient contact time is inherently limited by the level of resources currently available within the NHS, but diet reinforcement is likely needed more frequently than once per year and current guidelines fail to reflect this. An acceptable alternative to regular dietitian-led counselling may be to use short, diabetes-specific dietary screening tools suitable for delivery by non-nutrition experts to provide individualised advice targeted to those most in need [435].

Dietary pattern change in the first half of the Early-ACTID trial indicated that moving total carbohydrate and fat intakes towards meeting general UK healthy eating guidelines associated with improvements in glycaemic control, even after weight loss was taken into account. NICE guidelines, updated in 2022, continue to promote that dietary intakes for people with T2DM should be in line with healthy eating guidelines for the general population; a recommendation unchanged since 2009 [431]. The NICE guidelines specify diets should be higher in fibre, with carbohydrates coming chiefly from fruit, vegetables, wholegrains and pulses. Additionally, NICE highlights reducing saturated fats in general, opting for lower-fat dairy and consuming oily fish. Improvements (that is, increases) in 'carb/fat balance' dietary pattern scores coincide with these NICE recommendations for greater intakes of fibre, fruit, lower-fat dairy and legumes/pulses alongside reductions in saturated fats (higher-fat processed meats and butter/animal fats) and low-fibre (non-wholegrain) bread. NICE guidelines also do not specify macronutrient intakes *per se*, but by implication, recommending intakes around general healthy eating guidelines suggests ≥50% food energy should come from carbohydrates [349] and ≤35% food energy should come from fats [350]. NICE dietary recommendations for adults with T2DM thus coincide with evidence obtained from short-term analyses of the Early-ACTID trial.

Diabetes UK nutritional guidelines recommend a Mediterranean or equivalent style dietary patterns in T2DM, but primarily for the control of CVD-related risk factors [20]. These guidelines go on to specify such diets should be high in wholegrains, fruit, vegetables, fish, nuts and legumes and low in red and processed meat, refined carbohydrates and sugar-sweetened beverages. Alcohol and salt should be limited, saturated fat intakes replaced with unsaturated fats and two portions of oily fish consumed weekly [20]. Thus, although not recommended specifically for improving HbA1c over the short-term, current food-based guidelines from Diabetes UK are in line with evidence from study 1 linking the 'carb/fat balance' dietary pattern with improved health outcomes. The null findings in

this thesis between the 'carb/fat balance' dietary pattern and long-term glycaemic deterioration are in line with messaging within Diabetes UK guidelines; there is no evidence for a superior dietary approach for managing glycaemia over the long-term [20]. Long-term glycaemia and its relationships, or lack thereof, with diet composition is not addressed explicitly within the NICE guidelines discussed above [431]. A patient-centred approach facilitating achievable dietary change that reduces energy intakes is however recommended by all guidelines and is therefore in overall agreement with the findings of this thesis.

Weight loss was associated with improved glycaemic control during the Early-ACTID trial, as expected. Weight loss is therefore rightly recommended within all current T2DM guidelines for improving a variety of biomarkers relevant to T2DM management [20, 431, 432]. Over recent years, the ultimate goal in T2DM care has shifted towards the possibility of achieving disease remission, defined as achieving blood glucose levels below 48 mmol/mol (6.5%) for at least 6 months, without use of glucose-lowering medications [436]. The DiRECT remission trial demonstrated this was feasible through the use of very-low energy diets (VLED) that instigate marked weight loss (10-15kg) early in the disease course [70], with remission maintained provided weight regain was prevented or limited [71]. Following an approximately 12-week phase of VLED meal-replacement drinks, foods are reintroduced in line with a diet consisting of ~50% energy from carbohydrate and <35% energy from fat; that is, a diet in line with current UK healthy eating recommendations [349, 350], which appears appropriate based on findings from study 1 of this thesis. Diabetes UK nutritional guidelines promote substantial weight loss for overweight or obese people with T2DM to aim to achieve disease remission; largely based on results from the DiRECT trial [20]. NICE guidelines updated in 2022 however make no reference to the possibility of remission [431]. However, DiRECT's VLED intervention is still being piloted throughout the UK to assess suitability for provision within primary care [437]. Although the Early-ACTID intervention was not designed to produce disease remission, the degree of weight loss induced by a non-prescriptive approach was only mild (Mean [95%CI]: -2.3 [-2.7, -1.8] kg during 0-6 months). Achieving similar weight loss to that seen in DiRECT would however not be practical under non-prescriptive advice; it is a prescriptive intervention by nature. If remission can however be sustained through maintenance of weight loss, then a temporary VLED offers a potentially profound breakthrough for preventing progression of disease in early T2DM.

In conclusion, findings from this thesis do not suggest major changes are required to current dietetic or clinical practice when informed by current guidelines. Dietary patterns were not found to associate with long-term glycaemia in T2DM. Diet-based interventions that can reduce energy intakes to achieve and sustain weight loss are likely to be key for managing T2DM glycaemic

progression over the long-term, in line with current recommendations. The overall nutritional quality of a person's diet should however be maximised to maintain general health and for controlling other common CVD risk markers in this population.

7.3 Implications for future research

High quality dietary data that reflects true intakes are paramount in studies exploring associations between diet and health outcomes. A significant limitation affecting each study of this thesis is that dietary data was self-reported from four-day diet diaries in studies 1-3 and 24-hr diet records in study 4. Although measured repeatedly in the same persons over time in studies 1-4, self-reported dietary measures are known to potentially contain a high degree of measurement error due to misreporting bias. Single 24-hr diet records, in particular, are generally unsuitable for capturing usual diet as day-to-day dietary variation is not recorded, resulting in a potentially high level of random error between overall habitual intake (necessary for exploring diet's effects on long-term health) and the intake recorded on any particular day [410]. Four-day food diaries are potentially less affected by these apparent self-reporting biases relative to other self-report measures [139, 140], but estimated misreporting prevalence can still be high, as observed in study 4 (52% participants classed as under-reporting energy intake). The use of self-reported rather than objective measures of diet is a limitation applicable to the vast majority of epidemiological research conducted up to this point in time and is thus not specific to the work presented in this thesis. However, observational research will continue to be affected by such issues until more objective markers of dietary intake can be discovered and incorporated into diet-health analyses.

'Nutritional metabolomics' is an evolving discipline integrating nutrition with metabolomics data, with an overall aim to discover novel, objective biomarkers indicative of nutritional status or exposure [132]. The 'metabolome' describes the full metabolite profile in biological samples such as blood, urine or saliva at a given point in time. It is time-sensitive and can be influenced by many factors such as age, disease state and nutritional intake [438]. Several studies have identified metabolomic markers that are associated with specific food and food group consumption [439], but many metabolomic signatures remain insensitive, unspecific and unavailable for many nutrients and foods. In studies seeking to characterise the food metabolome, many consumed foods are highly correlated, with biomarkers being identified that are not specific to any particular food but to broader food groups. One example includes vitamin C, carotenoids and flavonoids being common to

many fruits and vegetables but not currently attributable to intake of any one fruit or vegetable [440]. The possibility of using metabolite signatures for studies investigating overall dietary patterns rather than intakes of specific foods is however promising, as differences in dietary patterns may be more easily observed through the relative concentrations of many hundreds of metabolites [441]. Although not yet suitable as a full replacement for self-reported dietary data, metabolomic profiling has already been shown to compliment the more subjective dietary assessment methods discussed in section 2.5 [442], showing promise as an adjunct for improving accuracy of current dietary assessment in the future.

Secondly, more frequent assessment of both diet and HbA1c is required for appropriately determining temporal relationships between them. Diet and HbA1c was assessed every 6 months during the Early-ACTID trial, dropping to every 12-months during follow-up. In DIRECT 2.2, diet was assessed every 18 months and HbA1c every 9-18 months. Dietary intakes can change by the day of the week as well as time of year and a greater number of repeated diet measures can theoretically be better able to capture this variation (assuming one can avoid recording fatigue and other forms of reporting bias). In particular, changes in dietary intake following or during an intervention may be inadequately captured by only a baseline and a 6-month measure as in Early-ACTID. There may be immediate, gradual or unstable changes made in dietary intakes when receiving an intervention, with some food intakes changing more rapidly or perhaps fluctuating depending on a person's ability to adhere with change. A dietary measure at 6 months post-baseline in Early-ACTID may not therefore be fully reflective of the quantity or quality of dietary changes that were made during 0-6 months. Likewise, HbA1c is a measure of mean blood glucose over the preceding 3-4 months, but it is weighted more heavily towards mean blood glucose values relatively closer to the point of measurement. That is, mean blood glucose from the month preceding HbA1c measurement contributes approximately 50% to the HbA1c value, whereas mean blood glucose from 3-4 months previously contributes only 10% [36]. Dietary changes in the month prior to HbA1c measurement will thus impact HbA1c to a greater degree than dietary intakes in the months prior. In summary, true relationships between diet and HbA1c could potentially be masked when there is temporal mismatch between the times at which these variables are measured and the periods of time which these measures are taken to reflect. Future observational research should thus be designed with a greater number of interim diet measures, with blood glucose potentially measured through continuous glucose monitoring to obtain a more comprehensive glycaemic profile or otherwise HbA1c measured at least every 3 months, perhaps with known blood or urine dietary biomarkers measured in addition to provide objective measures of intakes of certain, potentially target, foods or drinks.

Thirdly, work presented in this thesis exploring long-term glycaemia sought to assess the potential effects of nutrient-mediated dietary patterns derived using reduced-rank regression in T2DM. The choice of intermediates were pre-specified based on theoretical relationships between dietary intake and glycaemia. Reduced-rank regression is however a data-driven method, and the dietary pattern explaining maximal variation in intakes of the specified nutrient intermediates: starches and sugars, fibre, SFA, MUFA, and PUFA produced the 'carb/fat balance' dietary pattern. The derived 'carb/fat balance' dietary pattern scores correlated positively with total carbohydrate and negatively with total fat intakes and did not differentiate further by the quality of these nutrients. It was not possible therefore to explore potential effects on glycaemia of a dietary pattern higher in fibre and lower in starches/sugars, for example, or a pattern reflecting higher ratio of intakes of unsaturated to saturated fats, as this was not the pattern extrapolated from the data. If dietary patterns that capture such nutrient intake differences do not ordinarily arise from 'real-world' dietary intakes explored via data-driven methods, which they did not in people with T2DM in the UK and Northern Europe studied in this thesis, then RRR is unlikely to be a suitable method for answering questions relating to such patterns. However, given that RCT's are expensive and often difficult to perform, and primary results have often been presented following an intention-to-treat analysis regardless of intervention adherence, secondary analyses of previous trial data in which dietary intakes can be re-explored in the form of nutrient-mediated, data-driven dietary patterns may be able to provide valuable data from which to design future dietary trials in T2DM. Potentially guided by results indicating which dietary approaches may then be considered most promising, a multi-year RCT could then be developed to confirm or refute relationships between certain dietary patterns and long-term glycaemia. Dietary intakes (both self-reported and potentially objective measures) would require being monitored frequently to aim to better capture usual dietary intakes, as discussed above, ensuring also similarly frequent measurement of clinical, haematological, anthropometric and other lifestyle-related markers for maximising the potential for causal inference. Numerical measures of adherence to dietary interventions should also be included in statistical analyses, something often missing from the majority of dietary trials in T2DM.

A 4-year trial by Esposito et al [97] explored the impact of diet on the time to requiring glucose-lowering medications (described in more detail in sections 2.7.3.1 and 5.1) and found that following a Mediterranean diet rather than a low-fat diet led to a delay in the need for starting medications. However, it is unclear whether effects were independent of weight change, as people receiving the Mediterranean diet intervention also lost more weight versus people on the low-fat diet. Again, whether glycaemic deterioration might have been delayed by the Mediterranean diet *per se* or by its ability to have induced a greater amount of weight loss may appear largely academic. However,

understanding potential mechanisms of action of diet on long-term glycaemia aids with provision of the most appropriate dietary advice, reducing potential diet-related anxieties should specific diets be incompatible with the preferences of the patient. Secondary analysis of data from this trial could thus provide valuable insight. Given the benefits of the Mediterranean dietary pattern on CVD risk markers in people with and without T2DM, it would otherwise, or in turn, be scientifically and ethically justifiable to conduct a new, long-term RCT to explore whether the Mediterranean diet does indeed delay the rate of glycaemic deterioration independent of weight change, following the principles for a potential RCT outlined above.

This thesis was unable to explore the effects of low-carbohydrate diets on T2DM progression. Further research is necessary on whether low- or very low-carbohydrate diets could offer benefits to long-term glycaemia independent of weight loss. Carbohydrates are the chief dietary contributor to post-prandial glucose and lowered intakes can lead to a reduced need for glucose-lowering medications. Their potential use for preventing hyperglycaemia and the associated risk of CVD complications requires longer-term trials than exist currently. Such diets could however be useful for delaying progression to complications in people willing and able to follow such diets. However, a recent 6-week, weight-loss neutral RCT found that a moderate-carbohydrate, higher-protein diet (30% (energy from) CHO, 30% protein, 40% fat; n=34) led to reduced HbA1c and liver fat compared to a typical low-fat diet (50% CHO, 17% protein, 33% fat; n=33), but no benefits were observed between diets on pancreatic fat or beta-cell function [443, 444]. However, mean duration of disease in this trial was 7 years, potentially limiting the benefits achievable in beta-cell function by this time. In addition, diets did not meet the criteria for being classed as 'low-carbohydrate' (typically defined <26% energy from carbohydrate [417]) and the study was only of short duration. It remains unclear therefore whether beta-cell function would continue to deteriorate with a low-carbohydrate diet without weight loss. Longer-term trials are necessary to explore whether low-carbohydrate diets can reduce the incidence of CVD-related complications, even if beta-cell function itself continues to decline. As stated above, secondary analyses of data from low-carbohydrate diet trials in which dietary intakes can be re-explored in the form of nutrient-mediated, data-driven dietary patterns, using methods such as reduced-rank regression, may otherwise be valuable for providing clarity on physiological benefits attributable to the combined intakes of both nutrients and foods.

7.4 Conclusion

This thesis explored changes in data-driven, nutrient-mediated dietary patterns and whether they associated with short- and long-term changes in glycaemia in people recently diagnosed with T2DM. Four studies were conducted. The first study explored whether short-term changes in nutrient-mediated dietary patterns associated with glycaemic control independent of weight change during a dietary intervention. The second study explored the degree of change in nutrient-mediated dietary patterns during and following this dietary intervention, and whether changes differed between men and women. The third study explored whether nutrient-mediated dietary patterns associated with the rate of deterioration in glycaemia during long-term follow-up after a dietary intervention. The fourth study explored whether the association between nutrient-mediated dietary patterns and the rate of long-term glycaemic deterioration was consistent between different cohorts of people with recently-diagnosed T2DM.

A 'carb/fat balance' dietary pattern, so-called because it balanced carbohydrate and fat intakes around UK healthy eating guidelines, was derived from self-reported dietary data. Increases in this dietary pattern score shifted total carbohydrates higher and total fats lower and associated with small improvements in HbA1c concentrations independent of weight loss over 6 months. However, this dietary pattern did not associate with the rate of glycaemic deterioration observed within people recently-diagnosed with T2DM over the longer-term (periods up to 3-5 years), producing no evidence that dietary patterns might affect the rate of disease progression in T2DM. Furthermore, typical dietary interventions in T2DM do not lead to differential dietary pattern change over the short- or long-term between men and women, suggesting current interventions are equally suited to both sexes. However, maintenance of dietary pattern change is poor over the longer-term in both sexes.

The findings of this thesis are in agreement with current nutritional guidelines for the management of T2DM. Weight-loss should remain the primary focus through which people with T2DM can improve their glycaemic control. Future research in this area should adopt the use of more objective markers of usual dietary intake alongside more frequent measurement intervals of diet, glycaemia and multiple other potential confounding variables to better elucidate causal relationships between T2DM and lifestyle factors. Further research into the potential benefits of the Mediterranean and low-carbohydrate dietary patterns on the rate of glycaemic deterioration in early T2DM and incidence of complications is also recommended.

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Chapter 8 - Appendices

8.1 Supplementary Materials for Chapter 3 (Study 1)[2]

Information S8.1: Further details on dietary misreporting calculation

PAL categories were assigned based on baseline minutes of moderate-vigorous physical activity (MVPA) [344]. A 1-SD cut-off [345] around reported energy intake/estimated energy requirement (rEI/EER) (20% in men and 19% in women) was used assuming energy balance (rEI/EER=1.0) to allocate misreporting status as plausible (e.g. rEI/EER=0.8 to 1.2), under- (e.g. rEI/EER<0.80) or over-reporting (e.g. rEI/EER>1.20).

Information S8.2: Further details on sensitivity analyses

In *Model 1a*, we estimated the impact of having missing covariate data on the unadjusted estimate in model 1 by repeating the model in a restricted sample that had complete data on all covariates included in models 2-3. The effects of missing data versus confounder adjustment were differentiated by comparing changes in the β and 95% CI in models 1 to 1a (missing data effect i.e. same adjustment in a smaller sample) and models 1a to 2 (confounder adjustment effect i.e. different adjustment in the same sample). To estimate missing data bias in our analyses, we examined differences in sample characteristics owing to missing data on diet and covariates by comparing participants with complete data against the full Early-ACTID sample during each period.

To test assumptions of linearity, tests for trend between dietary pattern score change quintiles and their estimated marginal (HbA1c) means during each period were performed using a likelihood ratio test. This compared goodness of fit of modelling categorical (quintiles of) dietary pattern score change versus continuous score change in model 2. Potential interactions between dietary pattern and sex were also explored by including an interaction term between dietary pattern score change and sex in model 2.

[2] These supplementary materials were published alongside the primary study as, "Garbutt J, England C, Jones AG, Andrews RC, Salway R and Johnson L. Is glycaemic control associated with dietary patterns independent of weight change in people newly diagnosed with type 2 diabetes? Prospective analysis of the Early-ACTivity-In-Diabetes trial. BMC Medicine. 2022; 20:161. DOI: 10.1186/s12916-022-02358-5." The materials are presented as per the article. A small number of foods have been added to food groupings displayed in Table S8.1 to coincide with the additional dietary data explored in Chapters 4-6.

We believed including trial arm in our main analysis models would lead to model over-adjustment. The trial arm that participants had been assigned to was considered to lie earlier on the causal pathway potentially linking dietary change to HbA1c change, meaning it would not be confounding relationships between diet and HbA1c. Additionally, other targets of the intervention such as physical activity, energy intake and bodyweight changes were to be separately adjusted for within our models. However, to explore any effects of potential confounding by trial arm, models 2-3 were repeated with trial arm adjustment included.

To confirm relationships between weight change and HbA1c, we repeated models 1-2 for each period. *Model 1* estimated unadjusted associations between period weight change (exposure) and end-of-period HbA1c (outcome), adjusting for start-of-period HbA1c and weight. *Model 2* estimated associations independent of potential confounders by adjusting for age, sex, and period-change in total physical activity. Finally, we estimated associations of changes in dietary patterns (exposure) with end-of-period bodyweight (outcome) between 0-6m, 6-12m, or 0-12m (outcomes) using models 1-2 outlined above but adjusting for start-of-period weight instead of HbA1c. *Model 3* in these cases estimated mediation by adding TEI only.

Information S8.3: Code used for employing reduced-rank regression in Stata (via SAS).

Reduced Rank Regression of percentage energy from combined starches and sugars (percent_cho), fibre density (fd), percentage energy from saturated fat (percent_sfa), percentage energy from monounsaturated fat (percent_mufa), and percentage energy from polyunsaturated fat (percent_pufa) with all food groups (ave_grams_foodgroup1-ave_grams_foodgroup65)

```
plssas, y(percent_cho fd percent_sfa percent_mufa percent_pufa) x(ave_grams_foodgroup1-ave_grams_foodgroup65) method(rrr)
exe(C:\Program Files\SASHome\SASFoundation\9.4\sas.exe)
insheet using "N:\Stata output\out.csv", comma clear
save “PersonLevelFile_earlyactid_direct_RRR.dta", replace
```

Reduced Rank Regression of dietary energy density (ded), fibre density (fd) and percentage energy from fat (percent_fat) with all food groups (ave_grams_foodgroup1-ave_grams_foodgroup47)

```
plssas, y(ded fd percent_fat) x(ave_grams_foodgroup1-ave_grams_foodgroup47) method(rrr)
exe(C:\Program Files\SASHome\SASFoundation\9.4\sas.exe)
insheet using "N:\Stata output\out.csv", comma clear
save “PersonLevelFile_earlyactid_indirect_RRR.dta", replace
```

Table S8.1*:* Food groups and their contents for the 'obesogenic' and 'carb/fat balance' dietary patterns.

Obesogenic dietary pattern		**Carb/fat balance dietary pattern**	
Food group	**Contents**	**Food group**	**Contents**
Alcoholic drinks	Beer, cider, wine and spirits	**Alcoholic drinks**	Beer, cider, wine and spirits
Biscuits and cakes	Sweet biscuits (all types) including chocolate-covered, sweet buns, cakes and pastries (all sweet types), cereal bars	**Biscuits (sweet)**	Sweet biscuits (all types) including chocolate-covered
		Cakes	Sweet buns, cakes and pastries (all sweet types), cereal bars
Butter and animal fats	Full-fat and half-fat butter, lard/dripping	**Butter and animal fats**	Full-fat and half-fat butter, lard/dripping, palm oil, vegetable suet
Cereal based mixed meals	Pasta in sauce, pasta with cheese, pasta and rice salads, tabbouleh, risotto	**Cereal based mixed meals**	Pasta in sauce, pasta with cheese, pasta and rice salads, tabbouleh, risotto, egg-fried rice
Cheese	Cheeses and cheese spreads, including cottage cheese	**Cottage cheese**	Reduced-fat and full-fat cottage cheese: plain or with additions
		Other cheese	All cheese and cheese spreads other than cottage

			cheese
Chocolate and confectionery	Plain chocolate and chocolate-based confectionary, table sugar, syrups, sweets	**Chocolate**	Plain chocolate and chocolate-based confectionary
Spreads (sweet)	Honey, fruit-jams and curds	**Spreads (sweet) and confectionery**	Honey, fruit-jams and curds, table sugar, syrups, sweets
Coated chicken and fish	Fish or chicken in batter or breadcrumbs	**Coated chicken and fish**	Fish or chicken in batter or breadcrumbs
Condiments	Herbs, spices, stock cubes	**Condiments**	Herbs, spices, stock cubes
Sauces (low energy density < 10 kJ/g)	Water-, milk-, cheese-, vinegar-, vegetable-, or fruit-based sauces and dressings	**Sauces (low energy density < 10 kJ/g)**	Water-, milk-, cheese-, vinegar-, vegetable-, or fruit-based sauces and dressings
Boiled/baked potatoes	Boiled, mashed and baked potatoes, gnocchi	**Boiled/baked potatoes**	Boiled and baked potatoes, gnocchi
Crisps and savoury snacks	Potato, wheat-based, vegetable and corn crisps, pretzels, papadums	**Crisps and savoury snacks**	Potato, wheat-based, vegetable and corn crisps, pretzels, papadums
Eggs and egg dishes	Boiled/poached/fried/scrambled eggs, omelettes, quiches, egg-fried rice, egg	**Eggs**	Boiled/ poached/dry-fried/plain-scrambled eggs

	mayonnaise, Scotch eggs		
		Egg dishes	Egg mayonnaise, omelettes, fried and scrambled eggs
Fish	Fish; canned, boiled, steamed, poached, baked or grilled; plain or in pies or pastry, curry; not battered or breaded	**White fish and shellfish**	Non-oily fish; canned, boiled, steamed, poached, baked or grilled; not battered or breaded
		Oily fish	Canned, grilled, baked, or fried anchovies, herring, kipper, mackerel, pilchards, salmon, sardines, trout; not battered or breaded
		Fish and shellfish mixed dishes	Fisherman's pie, tuna mayonnaise, fish or shellfish curries, in sauce, pasta.
Fruit (fresh)	Fresh fruit, including canned in juice	**Fruit (fresh)**	Fresh fruit, including canned in juice
Fruit (other)	Stewed (with or without sugar), baked, dried, and canned in syrup	**Fruit (other)**	Dried fruit (all types)
Fried/roast vegetables	Fried or roasted vegetables, excluding	**Fried/roast vegetables**	Fried or roasted vegetables, excluding

	potatoes		potatoes
Fried/roast potatoes and chips	Fried or roast potatoes, chips, potato waffles	**Fried/roast, chips and other potato with added fat**	Fried, mashed or roast potatoes, chips, potato waffles, potato salad (with mayonnaise), cheese and potato 'pie'
Fruit juice	Fruit juice (all types), fruit smoothies	**Fruit juice**	Fruit juice (all types), fruit smoothies
High fat milk and cream	Fresh or powdered whole cow's or goat's milk, milkshakes, cream (all types), crème fraiche, evaporated/condensed milk	**High fat milk**	Fresh or powdered whole cow's or goat's milk, milkshakes
		Cream	Cream (all types), crème fraiche, evaporated/condensed milk
High fibre bread	Brown, wholemeal, granary, rye, white (with added fibre) bread or rolls	**High fibre bread**	Brown, wholemeal, granary, rye, white (with added fibre) bread or rolls
High fibre breakfast cereals	Bran- or wheat-based cereals, oatmeal/porridge, muesli	**High fibre breakfast cereals**	Bran- or wheat-based cereals, oatmeal/porridge; excluding muesli

		Muesli	Muesli (all types)
Hot and powdered drinks	Teas, coffees, malted drinks, hot chocolate, diet powder drinks	**Powdered drinks**	Instant coffees, malted drinks, hot chocolate
Low energy drinks	Fruit squashes or cordials and carbonated drinks with sweetener/no sugar added	**Low energy drinks (hot and cold)**	Fruit squashes or cordials and carbonated drinks with sweetener/no sugar added, black tea, black coffee, water
Water	Mineral, flavoured and tap water		
Ice-creams	All ice-cream-based desserts	**Ice-creams**	All ice-cream-based desserts
Legumes	Boiled, canned, baked-in-sauce beans and lentils	**Legumes**	Boiled, canned, baked-in-sauce beans, peas and lentils
Low fat milk	Skimmed/semi-skimmed fresh or powdered dairy milk, soya milk, powdered hot drinks made up with skimmed/semi-skimmed milk	**Low fat milk**	Skimmed/semi-skimmed fresh or powdered dairy milk, soya milk, powdered hot drinks made up with skimmed/semi-skimmed milk
Low fibre bread	White bread, bagels, breadcrumbs, rolls and tortillas	**Low fibre bread**	White bread, bagels, breadcrumbs, rolls and tortillas

Margarine and Vegetable oils	PUFA/non-PUFA spreads, cod liver oil, seed oils, palm oil, vegetable suet	**PUFA oils**	Vegetable oil, sunflower oil, cod liver oil
		MUFA oils	Olive oil, rapeseed oil
		PUFA spreads	Polyunsaturated spreads and margarines (35-70% fat), flora proactive
		Other spreads	Non-PUFA-based spreads and margarines
Meat and poultry	Beef, lamb, pork, chicken, duck, offal; stewed, fried, grilled or roasted	**Red meat**	Beef, lamb, pork, duck, game with fat; stewed, fried, grilled or roasted
		Lean red meat	Offal, lean beef, lamb or pork; fried, grilled or roasted
		Poultry	Chicken or turkey; stewed, fried or roasted
Meat mixed dishes	Meat and poultry in casseroles, curries, stews, Bolognese, lasagne, pies and pastries; excluding soups	**Poultry mixed dishes**	Chicken/turkey casserole, curry/in sauce, Bolognese; excluding soups
		Red meat mixed dishes	Beef, lamb, pork, or offal curries, stews, hotpots, Bolognese, lasagnes or cooked with vegetables;

			excluding soups.
		Savoury pies/pastries	Vegetable- or meat-based pies and pastries, including plain pastry and savoury suet pudding
Meat substitutes	Quorn, Soya mince, tofu and related products	**Meat substitutes**	Quorn, Soya mince, tofu and related products
Nuts and seeds	Nuts and seeds (all types) including coconut flesh	**Nuts and seeds**	Nuts and seeds (all types) including coconut flesh
Other bread products	Breads with added fat such as brioche, naan, garlic and fried. Dumplings, stuffing, Yorkshire puddings, savoury biscuits, bran, plain pastry	**Other bread products**	Breads with added fat such as brioche, naan, garlic and fried. Dumplings, stuffing, Yorkshire puddings
		Biscuits (savoury)	Breadsticks, crackers, crispbreads, oatcakes and rice cakes
Low fibre breakfast cereals	Corn flakes, Frosties, Rice Krispies, Special K	**Low fibre breakfast cereals**	Corn flakes, Frosties, Rice Krispies, Special K
Pizza	Pizza (all types)	**Pizza**	Pizza (all types)
Processed meat	Bacon, gammon, ham, burgers, corned beef, sausages, meat spreads	**Lower fat processed meats**	Lean bacon, gammon, ham, reduced-fat pork sausages, low-fat meat spreads and

	and paté, cured meats, meat loaf		patés, turkey ham
		Higher fat processed meats	Bacon, burgers, corned beef, sausages, meat spreads, full-fat pâté, cured meats; with no fat removed
		Processed meat mixed meals	Baked beans with sausages, burgers in buns, corned beef hash, scotch eggs, sausage casserole, toad in the hole, meat loaf
Puddings	Sweet pies, crumbles, tarts, meringues, cheesecakes, custards, pancakes, mousses, rice puddings, jellies, sponge puddings	**Puddings**	Sweet pies, crumbles, tarts, meringues, cheesecakes, custards, pancakes, mousses, rice puddings, jellies, sponge puddings, stewed fruit, fruit canned in syrup
Rice, pasta and other grains	White or brown rice, pasta, couscous, noodles, pearl barley, quinoa	**White rice, pasta and other grains**	White rice, pasta, couscous, noodles, pearl barley
		Whole-grain rice, pasta and other grains	Wheat-bran, brown rice, pasta, quinoa
Sauces (higher energy density > 10	Egg-, cream-, or oil-based sauces	**Sauces (higher energy density > 10**	Egg-, cream-, or oil-based sauces

kJ/g)		**kJ/g)**	
Soups	Soup (all types except stews)	**Soups**	Soup (all types except stews)
Reduced/sugar-free confectionery	Sugar-free/reduced-sugar sweets and chocolates, artificial sweeteners	**Reduced/sugar-free confectionery**	Sugar-free/reduced-sugar sweets, chocolates and sweet spreads, artificial sweeteners
Sugar-sweetened drinks	Fruit squashes or cordials and carbonated drinks with added sugar, energy drinks	**Sugar-sweetened drinks**	Fruit squashes or cordials and carbonated drinks with added sugar, energy drinks, diet powder drinks
Vegetable mixed dishes	Mixed vegetables in cheese-based sauces, curries, casseroles, chilli's, lasagne, pie's, flans, pastry, pâtés, falafel, guacamole, mayonnaise salads; excluding soups	**Vegetable mixed dishes**	Mixed vegetables in cheese-based sauces, curries, casseroles, chilli's, lasagne, shepherd's pie, pâtés, falafel, guacamole; mayonnaise salads; excluding soups
Vegetables (Raw/boiled/grilled)	Raw, pickled, grilled or boiled vegetables, sweet potato, avocado, peas	**Vegetables (Raw/boiled/grilled)**	Raw, pickled, grilled or boiled vegetables, sweet potato, avocado
Yoghurts	Plain and flavoured dairy/soya yoghurts, fromage frais, probiotic/drinking yoghurts	**Plain yoghurts**	Plain dairy/soya yoghurt, fromage frais

		Other yoghurts	Flavoured/fruit yoghurts and fromage frais, probiotic/drinking yoghurts

Table S8.2: Characteristics of all Early-ACTID participants compared with participants with complete covariate data for adjusted secondary analyses (periods 6-12m and 0-12m*)*.

Data marked in bold relates to variables used in analysis models for that period. Data presented as n (%) or median (Q1, Q3).

		n	Early-ACTID participant characteristics	n	6-12m participant characteristics with complete covariate data (models 1a-3)	n	0-12m participant characteristics with complete covariate data (models 1a-3)
n (%)			593 (100%)		194 (100%)		214 (100%)
Arm, n (%)							
	Usual care	593	99 (17%)	**194**	**9 (5%)**	**214**	**22 (10%)**
	Diet	593	248 (42%)	**194**	**93 (48%)**	**214**	**95 (44%)**
	Diet & Exercise	593	246 (41%)	**194**	**92 (47%)**	**214**	**97 (45%)**
Male, n (%)		593	383 (65%)	**194**	**136 (70%)**	**214**	**151 (71%)**
White ethnicity, n (%)		593	567 (96%)	194	189 (97%)	214	210 (98%)
Smoker at 0 months, n (%)		593	48 (8%)	194	13 (7%)	214	14 (7%)
Age at 0 months, years		592	61 (53, 68)	**194**	**63 (58, 69)**	**214**	**63 (57, 69)**
Time since diagnosis at 0 months, years		592	0.5 (0.4, 0.6)	194	0.5 (0.4, 0.6)	214	0.5 (0.4, 0.6)
IMD score at 0 months		591	12.7 (7.2, 20.0)	193	12.6 (6.3, 19.1)	213	12.6 (6.5, 19.1)
Total activity at 0 months, counts/min		546	286 (218, 366)	184	293 (222, 369)	**214**	**291 (221, 367)**
Total activity at 6 months, counts/min		495	298 (218, 395)	**194**	**332 (226, 409)**	200	330 (223, 406)
Total activity change 0-6m, counts/min		461	9 (-44, 75)	184	22 (-42, 93)	200	10 (-43, 86)
Total activity change 6-12m, counts/min		415	-4 (-61, 49)	**194**	**-3 (-72, 45)**	200	-1 (-71, 47)
Total activity change 0-12m, counts/min		429	2 (-51, 67)	184	2 (-49, 81)	**214**	**2 (-52, 78)**
MVPA at 0 months, mins/day		546	21 (12, 36)	184	23 (13, 37)	**214**	**22 (11, 37)**
MVPA at 6 months, mins/day		495	25 (12, 43)	**194**	**32 (15, 48)**	200	30 (14, 48)
MVPA change 0-6m, mins/day		461	2 (-7, 11)	184	3 (-5, 19)	200	2 (-7, 18)
MVPA change 6-12m, mins/day		415	-1 (-9, 6)	**194**	**-1 (-11, 5)**	200	-1 (-10, 5)
MVPA change 0-12m, mins/day		429	0 (-8, 12)	184	1 (-9, 15)	**214**	**0 (-8, 14)**

Weight at 0 months, kg		592	89.0, (80.0, 99.3)	194	86.1 (77.9, 94.1)	**214**	**86.9 (78.6, 95.7)**
Weight at 6 months, kg		579	87.1 (77.7, 98.4)	**194**	**83.9 (75.2, 92.0)**	214	84.6 (75.8, 94.1)
Weight change 0-6m, kg		578	-1.3 (-3.4, 0.6)	194	-2.1 (-4.0, -0.2)	214	-2.1 (-3.8, -0.2)
Weight change 6-12m, kg		562	0.3 (-1.2, 2.0)	**194**	**0.1 (-1.3, 1.8)**	214	0.2 (-1.4, 1.9)
Weight change 0-12m, kg		564	-0.9 (-3.6, 1.3)	194	-1.8 (-5.1, 0.2)	**214**	**-1.5 (-4.8, 0.8)**
BMI at 0 months, kg/m2		592	30.4 (27.8, 34.2)	194	29.3 (27.3, 32.6)	**214**	**29.3 (27.3, 33.0)**
BMI at 6 months, kg/m2		579	29.6 (27.2, 33.6)	**194**	**28.6 (26.4, 32.0)**	214	28.7 (26.5, 32.4)
BMI change 0-6m, kg/m2		578	-0.5 (-1.2, 0.2)	194	-0.7 (-1.4, -0.1)	214	-0.7 (-1.3, -0.1)
BMI change 6-12m, kg/m2		562	0.1 (-0.4, 0.7)	**194**	**0.0 (-0.5, 0.6)**	214	0.1 (-0.5, 0.7)
BMI change 0-12m, kg/m2		564	-0.3 (-1.2, 0.4)	194	-0.6 (-1.8, 0.1)	**214**	**-0.5 (-1.6, 0.3)**
HbA1c at 0 months, mmol/mol		593	48 (43, 54)	194	48 (43, 54)	**214**	**48 (43, 54)**
HbA1c at 0 months, %		593	6.5 (6.1, 7.1)	194	6.5 (6.1, 7.1)	**214**	**6.5 (6.1, 7.1)**
HbA1c at 6 months, mmol/mol		569	47 (42, 53)	**194**	**45 (41, 51)**	213	45 (41, 51)
HbA1c at 6 months, %		569	6.4 (6.0, 7.0)	**194**	**6.3 (5.9, 6.8)**	213	6.3 (5.9, 6.8)
HbA1c change 0-6m, mmol/mol		569	-1.1 (-4.4, 3.3)	194	-2.2 (-6.6, 1.1)	213	-2.2 (-5.5, 2.2)
HbA1c change 0-6m, %		569	-0.1 (-0.4, 0.3)	194	-0.2 (-0.6, 0.1)	213	-0.2 (-0.5, 0.2)
HbA1c change 6-12m, mmol/mol		560	1.1 (-2.2, 3.3)	**194**	**0.0 (-2.2, .2)**	213	0.0 (-2.2, 2.2)
HbA1c change 6-12m, %		560	0.1 (-0.2, 0.3)	**194**	**0.0 (-0.2, 0.2)**	213	0.0 (-0.2, 0.2)
HbA1c change 0-12m, mmol/mol		574	-1.1 (-4.4, 4.4)	194	-2.2 (-6.0, 1.1)	**214**	**-2.2 (-6.0, 2.2)**
HbA1c change 0-12m, %		574	-0.1 (-0.4, 0.4)	194	-0.2 (-0.5, 0.1)	**214**	**-0.2 (-0.5, 0.2)**
OHA prescription at 0 months, n (%)							
	Metformin	593	206 (35%)	194	66 (34%)	214	74 (35%)
	Sulphonylurea	593	50 (8%)	194	15 (8%)	214	18 (8%)
	Glitazone	593	7 (1%)	194	2 (1%)	214	2 (1%)
OHA prescription from 6 months, n (%)							
	Metformin	593	209 (35%)	194	66 (34%)	214	74 (35%)
	Sulphonylurea	593	53 (9%)	194	15 (8%)	214	19 (9%)
	Glitazone	593	9 (2%)	194	2 (1%)	214	3 (1%)

IMD – index of multiple deprivation; MVPA – moderate-vigorous physical activity; OHA - oral-hypoglycaemic agent.

Table S8.3: Explained nutrient variation and correlations for 'carb/fat balance' dietary patterns derived at 0, 6 and 12-months.

	Explained variation (%)							Correlation coefficient				
Timepoint	**Nutrient intake (total)**	**Starches and sugars (%)**	**Fibre density (g/MJ)**	**SFA (%)**	**MUFA (%)**	**PUFA (%)**	**Food intake (total)**	**Starches and sugars (%)**	**Fibre density (g/MJ)**	**SFA (%)**	**MUFA (%)**	**PUFA (%)**
0 months	36.2	53.9	45.1	40.9	39.9	1.4	2.1	0.74	0.68	-0.64	-0.63	-0.12
6 months	39.2	57.5	47.4	45.7	44.2	1.1	2.4	0.76	0.69	-0.68	-0.67	-0.10
12 months [a]	40.0	57.0	45.2	44.5	51.1	2.3	2.7	-0.75	-0.67	0.67	0.71	0.15

SFA - saturated fat; MUFA - mono-unsaturated fat; PUFA - poly-unsaturated fat.

[a] A congruence coefficient between dietary patterns at separate timepoints of ≥0.95, 0.85-0.94, or <0.85 suggest good, fair, or unacceptable similarity respectively [342]. We calculated a congruence coefficient of 0.89 between 0- and 6-month dietary patterns. However, a negative congruence coefficient was obtained for 0 and 12-month dietary patterns (congruence coefficient: -0.87). This coincided with equal in magnitude, but opposing in sign, dietary pattern-nutrient correlations at these timepoints. Given 'fair' pattern structural similarity, the independently derived 12-month dietary pattern scores were interpreted as essentially being 'inverted' baseline pattern scores as an artefact of the reduced-rank regression's final iteration. Multiplying all food group pattern loadings at 12 months by -1 moved the direction of association of the dietary pattern score with its nutrient response variables to be in line with those seen at 0 months. Projecting this single, 0-month dietary pattern structure onto 6 and 12-month data thus allowed for a meaningful analysis of changes in a single dietary pattern score over time.

Table S8.4: Explained nutrient variation and nutrient correlations for energy-dense, higher-fat, lower-fibre 'obesogenic' dietary patterns derived at 0, 6 and 12 months.

Congruence coefficients equalled 0.90 between 0-months and both 6- and 12-month dietary patterns.

	Explained variation (%)					Correlation coefficient		
Timepoint	**Nutrient intakes (total)**	**DED (g/kJ)**	**Fat (%)**	**Fibre density (g/MJ)**	**Food intake (total)**	**DED (g/kJ)**	**Fat (%)**	**Fibre density (g/MJ)**
0 months	51.3	66.7	35.9	51.2	3.4	0.81	0.60	-0.72
6 months	58.1	73.3	44.4	56.5	3.6	0.86	0.67	-0.75
12 months	58.1	70.4	47.0	56.9	3.8	0.84	0.69	-0.75

DED – dietary energy density.

Table S8.5: Descriptive dietary and sample characteristics in extreme quintiles of 'carb/fat balance' dietary pattern score change during 0-6m.

Participants in quintile 5 made the greatest change towards higher-carb, lower-fat intakes during 0-6 months (mean change: 1.25, SD 0.42). Participants in quintile 1 made the least dietary change in this direction (mean change: -0.91, SD 0.46; suggesting average participant dietary intakes in this quintile became lower in carbohydrate and higher in fat compared to baseline intakes). All other data presented as n (%) or median (Q1, Q3). Highest loading food group intakes in median (Q1, Q3) g/day are presented to indicate the average amounts (and change in amounts) of foods consumed. Percentage of consumers (and change in consumers) of these food groups indicate the number of (and change in number of) individuals consuming any amount of these foods. Median 'Meat substitutes' intake is zero, for example, but should be interpreted in context of percentage of consumers being very low (2% of whole sample).

Highest and lowest quintile sample characteristics (models 1a-3) of 0-6m 'carb/fat balance' dietary pattern score change			
	Whole sample	**Quintile 1**	**Quintile 5**
n	242	49	48
Carb/fat balance dietary pattern score at baseline, SD	0.04±0.79	0.66±0.72	-0.67±0.69
Carb/fat balance dietary pattern score change 0-6m, SD	0.12±0.78	-0.91±0.46	1.25±0.42
TEI at baseline, kJ	7347 (6220, 8619)	7464 (6166, 8413)	8055 (6770, 9170)
TEI change 0-6m, kJ	-731 (-1647, -6)	-367 (-1640, 54)	-1078 (-1922, -445)
Starches and sugars at baseline, %TEI	43.5 (39.8, 48.1)	46 (42.7, 51.2)	40.3 (35.6, 43.2)
Starches and sugars change 0-6m, %TEI	0.6 (-3.3, 5.3)	-5.3 (-7.8, -1.4)	6.8 (2.5, 9.2)
Fibre density at baseline, g/MJ	2.3 (1.9, 2.6)	2.5 (2.2, 2.8)	2.1 (1.6, 2.4)
Fibre density change 0-6m, g/MJ	0.1 (-0.2, 0.5)	-0.2 (-0.5, 0.1)	0.5 (0.1, 1.0)
SFA at baseline, %TEI	11 (9.5, 13.1)	9.9 (8.8, 11.5)	12.6 (10.5, 16.1)
SFA change 0-6m, %TEI	0.1 (-2.1, 1.8)	1.8 (0.2, 3.4)	-2.5 (-5.2, -0.4)
MUFA at baseline, %TEI	12.1 (10.5, 13.7)	10.9 (9.4, 12.7)	13.6 (11.4, 15)
MUFA change 0-6m, %TEI	0.2 (-1.5, 2.0)	1.8 (0.9, 3.5)	-1.7 (-3.3, 0.2)
PUFA at baseline, %TEI	6.4 (5.3, 7.8)	6.0 (5.0, 7.2)	6.6 (5.1, 7.9)
PUFA change 0-6m, %TEI	0.1 (-1.4, 1.6)	0.4 (-1.1, 2.4)	0.1 (-1.4, 2.1)
Total fat at baseline, %TEI	33.8 (30.3, 37.0)	30.5 (25.8, 34.8)	36.9 (33.6, 39.8)
Total fat change 0-6m, %TEI	0.1 (-3.8, 3.7)	4.7 (2.0, 8.3)	-4.6 (-8.0, -1.7)
Total carbohydrate at baseline, %TEI	45.4 (41.4, 49.9)	48.1 (44.6, 53.6)	41.9 (37.1, 44.8)
Total carbohydrate change 0-6m, %TEI	0.7 (-3.1, 5.4)	-5.6 (-7.9, -1.8)	7.3 (2.9, 9.7)

Positive factor loading food group intakes				
Fruit (fresh) at baseline, g/d		165 (96, 246)	181 (132, 288)	144 (67, 241)
	% consumers at baseline	*93*	*96*	*85*
Fruit (fresh) change 0-6m, g/d		-17 (-60, 51)	-46 (-147, -22)	47 (-24, 134)
	% consumers change 0-6m	*2*	*0*	*9*
Low fat milk at baseline, g/d		182 (118, 253)	192 (130, 250)	185 (91, 255)
	% consumers at baseline	*92*	*94*	*94*
Low fat milk change 0-6m, g/d		-13 (-60, 48)	-32 (-104, 28)	15 (-42, 87)
	% consumers change 0-6m	*3*	*-2*	*2*
Boiled/baked potatoes at baseline, g/d		44 (0, 83)	70 (38, 100)	25 (0, 64)
	% consumers at baseline	*72*	*82*	*54*
Boiled/baked potatoes change 0-6m, g/d		0 (-35, 46)	-15 (-47, 31)	16 (0, 53)
	% consumers change 0-6m	*5*	*-4*	*25*
Legumes at baseline, g/d		18 (0, 48)	19 (0, 53)	17 (0, 31)
	% consumers at baseline	*69*	*63*	*63*
Legumes change 0-6m, g/d		0 (-17, 20)	0 (-26, 18)	7 (-1, 40)
	% consumers change 0-6m	*2*	*-6*	*18*
Meat substitutes at baseline, g/d		0 (0, 0)	0 (0, 0)	0 (0, 0)
	% consumers at baseline	*2*	*2*	*0*
Meat substitutes change 0-6m, g/d		0 (0, 0)	0 (0, 0)	0 (0, 0)
	% consumers change 0-6m	*0*	*2*	*2*
Negative factor loading food group intakes				
Higher fat processed meats at baseline, g/d		10 (0, 30)	0 (0, 23)	17 (0, 41)
	% consumers at baseline	*56*	*49*	*60*
Higher fat processed meats change 0-6m, g/d		0 (-15, 12)	0 (-10, 15)	0 (-31, 7)
	% consumers change 0-6m	*0*	*8*	*-12*
Butter and animal fats at baseline, g/d		0 (0, 0)	0 (0, 0)	0 (0, 11)
	% consumers at baseline	*23*	*14*	*44*
Butter and animal fats change 0-6m, g/d		0 (0, 0)	0 (0, 0)	0 (-7, 0)
	% consumers change 0-6m	*0*	*13*	*-25*
Red meat at baseline, g/d		16 (0, 35)	15 (0, 27)	26 (0, 56)

% consumers at baseline	*54*	*53*	*65*
Red meat change 0-6m, g/d	-159 (-241, -91)	-160 (-241, -93)	-154 (-233, -77)
% consumers change 0-6m	*3*	*8*	*-7*
Low fibre bread at baseline, g/d	2 (0, 35)	0 (0, 28)	20 (0, 34)
% consumers at baseline	*50*	*45*	*63*
Low fibre bread change 0-6m, g/d	0 (-23, 0)	0 (-8, 0)	-5 (-28, 0)
% consumers change 0-6m	*-14*	*-14*	*-23*
Fried/roast, chips & other potato with added fat at baseline, g/d	36 (0, 68)	18 (0, 50)	39 (0, 75)
% consumers at baseline	*68*	*57*	*71*
Fried/roast, chips & other potato with added fat change 0-6m, g/d	0 (-34, 13)	0 (-14, 13)	-6 (-48, 8)
% consumers change 0-6m	*-6*	*4*	*-19*
Age at baseline, years	62 (57, 69)	63 (57, 71)	61 (56, 65)
Time since diagnosis at baseline, years	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)
Male, n (%)	163 (67%)	31 (63%)	37 (77%)
Under-reporting at baseline, n (%)	135 (56%)	24 (49%)	20 (42%)
IMD at baseline	12.6 (6.4, 18.9)	11.9 (6.4, 16.7)	13.6 (5.9, 20.9)
HbA1c at baseline, mmol/mol	47 (43, 54)	48 (44, 54)	45 (40, 55)
HbA1c at baseline, %	6.5 (6.1, 7.1)	6.5 (6.2, 7.1)	6.3 (5.9, 7.2)
HbA1c change 0-6m, mmol/mol	-2.2 (-5.5, 3.3)	-1.1 (-4.4, 2.2)	-2.2 (-6.6, 4.9)
HbA1c change 0-6m, %	-0.2 (-0.5, 0.3)	-0.1 (-0.4, 0.2)	-0.2 (-0.6, 0.5)
Weight at baseline, kg	86.6 (77.1, 94)	86.5 (78.9, 92.6)	82.7 (75.1, 93.6)
Weight change 0-6m, kg	-2.1 (-3.9, -0.1)	-1.9 (-3.3, 0.0)	-2.9 (-5.1, -0.9)
BMI at baseline, kg/m^2	29.5 (27.3, 32.7)	29 (26.8, 32.9)	29.3 (27.2, 32.8)
BMI change 0-6m, kg/m^2	-0.7 (-1.4, 0)	-0.6 (-1.2, 0.0)	-1.1 (-2.1, -0.3)
Total physical activity at baseline, counts/min	291 (226, 363)	286 (210, 348)	308 (256, 390)
Total physical activity change 0-6m, counts/min	16 (-44, 91)	18 (-42, 66)	37 (-31, 115)
MVPA at baseline, mins/day	21 (13, 36)	19 (13, 37)	25 (16, 39)
MVPA change 0-6m, mins/day	3 (-6, 18)	0 (-8, 12)	7 (0, 24)
Metformin, n (%)	85 (35%)	11 (22%)	17 (35%)
Metformin, %max dose	0 (0, 50)	0 (0, 0)	0 (0, 50)
Sulphonylurea, n (%)	22 (9%)	5 (10%)	6 (13%)

Sulphonylurea, %max dose	0 (0, 0)	0 (0, 0)	0 (0, 0)
Glitazone, n (%)	2 (1%)	0 (0%)	0 (0%)
Glitazone, %max dose	0 (0, 0)	0 (0, 0)	0 (0, 0)

TEI – total energy intake; SFA – saturated fat; MUFA – monounsaturated fat; PUFA – polyunsaturated fat; IMD – index of multiple deprivation; MVPA – moderate-vigorous physical activity.

Table S8.6: Descriptive dietary and sample characteristics by quintile of 'obesogenic' dietary pattern score change during 0-6m.

Participants in quintile 1 made the greatest change towards less energy-dense, lower-fat, higher-fibre intakes during 0-6 months (mean score change: -1.52, SD 0.44). Participants in quintile 5 made the least dietary change in this direction (mean change: 1.08, SD 0.44; suggesting average participant dietary intakes in this quintile became more energy-dense, higher in fat and lower in fibre compared to baseline intakes). All other data presented as n (%) or median (Q1, Q3). Highest loading food group intakes in median (Q1, Q3) g/day are presented to indicate the average amounts (and change in amounts) of foods consumed. Percentage of consumers (and change in consumers) of these food groups indicate the number of (and change in number of) individuals consuming any amount of these foods. Median 'Meat substitutes' intake is zero, for example, but should be interpreted in context of percentage of consumers being very low (2% of whole sample).

Highest and lowest quintile sample characteristics (models 1a-3) of 0-6m 'obesogenic' dietary pattern score change			
	Whole sample	**Quintile 1**	**Quintile 5**
N	242	49	48
Obesogenic dietary pattern score at baseline, SD	-0.05±0.97	0.71±0.84	-0.71±0.91
Obesogenic dietary pattern score change 0-6m, SD	-0.24±0.94	-1.52±0.44	1.08±0.44
TEI at baseline, kJ	7347 (6220, 8619)	8175 (6910, 9574)	7466 (6525, 8591)
TEI change 0-6m, kJ	-731 (-1647, -6)	-1072 (-2036, -321)	-272 (-1368, 538)
DED at baseline, kJ/g	6.3 (5.6, 7.1)	7.2 (6.4, 7.8)	5.8 (5.3, 6.4)
DED change 0-6m, kJ/g	-0.3 (-1.0, 0.5)	-1.5 (-1.8, -0.9)	0.8 (0.3, 1.3)
Fibre density at baseline, g/MJ	2.3 (1.9, 2.6)	2.0 (1.7, 2.4)	2.4 (2.1, 2.7)
Fibre density change 0-6m, g/MJ	0.1 (-0.2, 0.5)	0.7 (0.4, 1.0)	-0.3 (-0.6, 0.0)
Total fat at baseline, %TEI	33.8 (30.3, 37.0)	35.8 (34.3, 39.0)	33.4 (28.4, 35.8)
Total fat change 0-6m, %TEI	0.1 (-3.8, 3.7)	-3.8 (-6.6, 0.1)	2.6 (0.1, 7.0)
Total carbohydrate at baseline, %TEI	45.4 (41.4, 49.9)	42.8 (38.5, 45.8)	46.4 (43.0, 50.8)
Total carbohydrate change 0-6m, %TEI	0.7 (-3.1, 5.4)	5.5 (0.2, 9.3)	-2.5 (-6.8, 1.5)
SFA at baseline, %TEI	11.0 (9.5, 13.1)	11.9 (10.4, 15.5)	10.8 (9.4, 12.2)
SFA change 0-6m, %TEI	0.1 (-2.1, 1.8)	-1.6 (-3.7, 0.2)	0.3 (-1.2, 3.0)
Positive factor loading food group intakes			
Low fibre bread at baseline, g/d	2 (0, 35)	18 (0, 33)	0 (0, 21)
% consumers at baseline	*50*	*57*	*33*
Low fibre bread change 0-6m, g/d	0 (-23, 0)	-5 (-30, 0)	0 (0, 1)
% consumers change 0-6m	*-14*	*-24*	*2*

Processed meat at baseline, g/d		27 (9, 51)	28 (11, 51)	23 (3, 54)
	% consumers at baseline	*82*	*76*	*75*
Processed meat change 0-6m, g/d		-1 (-23, 15)	4 (-16, 15)	0 (-28, 31)
	% consumers change 0-6m	*1*	*10*	*0*
Coated chicken & fish at baseline, g/d		0 (0, 0)	0 (0, 0)	0 (0, 0)
	% consumers at baseline	*21*	*22*	*17*
Coated chicken & fish change 0-6m, g/d		0 (0, 0)	0 (0, 0)	0 (0, 0)
	% consumers change 0-6m	*-3*	*-2*	*6*
Fried/roast potatoes & chips at baseline, g/d		25 (0, 49)	33 (0, 50)	25 (0, 47)
	% consumers at baseline	*60*	*65*	*52*
Fried/roast potatoes & chips change 0-6m, g/d		0 (-26, 13)	0 (-30, 13)	0 (-12, 15)
	% consumers change 0-6m	*-7*	*-10*	*0*
Biscuits & cakes at baseline, g/d		14 (0, 33)	19 (4, 37)	8 (0, 29)
	% consumers at baseline	*71*	*78*	*58*
Biscuits & cakes change 0-6m, g/d		0 (-17, 7)	-5 (-21, 1)	0 (-9, 18)
	% consumers change 0-6m	*-9*	*-13*	*7*
Negative factor loading food group intakes				
Fruit (fresh) at baseline, g/d		165 (96, 246)	122 (63, 229)	185 (103, 289)
	% consumers at baseline	*93*	*94*	*96*
Fruit (fresh) change 0-6m, g/d		-17 (-60, 51)	69 (0, 138)	-56 (-170, -19)
	% consumers change 0-6m	*2*	*2*	*-2*
Vegetables (Raw/boiled/grilled) at baseline, g/d		120 (88, 173)	104 (83, 147)	138 (89, 211)
	% consumers at baseline	*99*	*100*	*98*
Vegetables (Raw/boiled/grilled) change 0-6m, g/d		5 (-42, 56)	57 (0, 101)	-34 (-60, 4)
	% consumers change 0-6m	*0*	*-2*	*0*
Yoghurts at baseline, g/d		0 (0, 61)	0 (0, 31)	31 (0, 91)
	% consumers at baseline	*46*	*39*	*65*
Yoghurts change 0-6m, g/d		0 (-13, 15)	0 (0, 20)	0 (-31, 3)
	% consumers change 0-6m	*-1*	*0*	*-11*
Boiled/baked potatoes at baseline, g/d		55 (30, 92)	44 (0, 75)	66 (39, 101)
	% consumers at baseline	*81*	*67*	*81*

Boiled/baked potatoes change 0-6m, g/d		0 (-38, 45)	21 (0, 48)	-13 (-49, 35)
	% consumers change 0-6m	*4*	*21*	*0*
Meat substitutes at baseline, g/d		0 (0, 0)	0 (0, 0)	0 (0, 0)
	% consumers at baseline	*2*	*2*	*2*
Meat substitutes change 0-6m, g/d		0 (0, 0)	0 (0, 0)	0 (0, 0)
	% consumers change 0-6m	*0*	*-2*	*2*
Age at baseline, years		62 (57, 69)	61 (55, 66)	61 (53, 68)
Time since diagnosis at baseline, years		0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)
Male, n (%)		163 (67%)	36 (73%)	31 (65%)
Under-reporting at baseline, n (%)		135 (56%)	21 (43%)	25 (52%)
IMD at baseline		12.6 (6.4, 18.9)	12.8 (6.3, 20.5)	8.3 (5.4, 17.6)
HbA1c at baseline, mmol/mol		47 (43, 54)	47 (43, 52)	49 (44, 57)
HbA1c at baseline, %		6.5 (6.1, 7.1)	6.4 (6.1, 6.9)	6.6 (6.2, 7.4)
HbA1c change 0-6m, mmol/mol		-2.2 (-5.5, 3.3)	-2.2 (-6.6, 3.3)	-1.1 (-6.6, 2.7)
HbA1c change 0-6m, %		-0.2 (-0.5, 0.3)	-0.2 (-0.6, 0.3)	-0.1 (-0.6, 0.2)
Weight at baseline, kg		86.6 (77.1, 94.0)	88.1 (75.5, 95.0)	85.8 (78.2, 93.6)
Weight change 0-6m, kg		-2.1 (-3.9, -0.1)	-2.4 (-4.5, -0.4)	-1.6 (-3.1, 1.1)
BMI at baseline, kg/m^2		29.5 (27.3, 32.7)	29.4 (26.5, 32.3)	29.2 (26.7, 33)
BMI change 0-6m, kg/m^2		-0.7 (-1.4, 0.0)	-0.8 (-1.5, -0.1)	-0.5 (-1.1, 0.4)
Total physical activity at baseline, counts/min		291 (226, 363)	302 (244, 356)	294 (241, 352)
Total physical activity change 0-6m, counts/min		16 (-44, 91)	35 (-2, 117)	4 (-66, 66)
MVPA at baseline, mins/day		21 (13, 36)	23 (14, 37)	25 (16, 42)
MVPA change 0-6m, mins/day		3 (-6, 18)	7 (-3, 25)	-2 (-9, 10)
Metformin, n (%)		85 (35%)	20 (41%)	15 (31%)
Metformin, %max dose		0 (0, 50)	0 (0, 50)	0 (0, 50)
Sulphonylurea, n (%)		22 (9%)	7 (14%)	5 (10%)
Sulphonylurea, %max dose		0 (0, 0)	0 (0, 0)	0 (0, 0)
Glitazone, n (%)		2 (1%)	0 (0%)	0 (0%)
Glitazone, %max dose		0 (0, 0)	0 (0, 0)	0 (0, 0)

TEI – total energy intake; DED – dietary energy-density; SFA – saturated fat; IMD – index of multiple deprivation; MVPA – moderate-vigorous physical activity.

Table S8.7: Relation between change in HbA1c (mmol/mol) and change in dietary pattern scores during study periods.

β is the change in end-of-period HbA1c associated with a 1-SD positive increase in dietary pattern score during period.

			Carb/fat balance pattern			Obesogenic pattern		
Timepoint	**Model**	**n**	**β**	**95%CI**	**p**	**β**	**95%CI**	**p**
0-6 months	*1*	280	-2.16	-3.42, -0.91	**0.001**	1.04	0.01, 2.07	**0.047**
	1a	242	-2.27	-3.69, -0.84	**0.002**	1.17	0.02, 2.33	**0.046**
	2	242	-2.21	-3.65, -0.78	**0.003**	1.06	-0.10, 2.23	0.074
	3	242	-1.54	-2.96, -0.13	**0.033**	0.63	-0.52, 1.78	0.283
6-12 months	*1*	229	-0.42	-1.47, 0.62	0.426	0.26	-0.66, 1.17	0.580
	1a	194	-0.25	-1.38, 0.88	0.663	0.09	-0.88, 1.06	0.854
	2	194	-0.46	-1.61, 0.68	0.427	0.17	-0.81, 1.16	0.727
	3	194	-0.61	-1.83, 0.60	0.321	0.28	-0.76, 1.33	0.591
0-12 months	*1*	256	-1.31	-2.34, -0.27	**0.014**	0.80	-0.09, 1.70	0.079
	1a	214	-0.68	-1.82, 0.46	0.240	0.48	-0.50, 1.46	0.335
	2	214	-0.86	-2.00, 0.28	0.139	0.60	-0.40, 1.59	0.237
	3	214	-0.78	-2.02, 0.45	0.212	0.51	-0.53, 1.55	0.335

1 – linear regression adjusted for start-of-period HbA1c and dietary pattern score in those with complete HbA1c and dietary pattern data during period.
1a – model 1 in sample restricted to those with complete covariate data.
2 – model 1a adjusted for age, sex, baseline under-reporting, change in OHA medications (metformin, sulphonylurea and glitazones separately in percentages of maximum dose) and change in total physical activity during period.
3 – model 2 adjusted for change in TEI and bodyweight during period (potential mediators between dietary pattern and HbA1c change).

Table S8.8: Relation between change in HbA1c (mmol/mol) and change in bodyweight during study periods.

β is the change in end-of-period HbA1c associated with a 1kg increase in bodyweight during period.

Timepoint	Model	n	β	95%CI	p
0-6 months	*1*	564	0.85	0.68, 1.03	**<0.001**
	1a	242	0.72	0.47, 0.97	**<0.001**
	2	242	0.70	0.45, 0.95	**<0.001**
6-12 months	*1*	549	0.17	-0.04, 0.37	0.121
	1a	194	0.11	-0.23, 0.45	0.524
	2	194	0.07	-0.27, 0.41	0.670
0-12 months	*1*	559	0.45	0.31, 0.60	**<0.001**
	1a	214	0.41	0.22, 0.60	**<0.001**
	2	214	0.37	0.17, 0.56	**<0.001**

1 – linear regression adjusted for start-of-period bodyweight and HbA1c in those with complete bodyweight and HbA1c data during period.
1a – model 1 in sample restricted to those with complete covariate and diet pattern data.
2 – model 1a adjusted for age, sex and change in total physical activity during period.

Table S8.9: Relation between change in bodyweight (kg) and change in dietary pattern score during study periods.

β is the change in end-of-period bodyweight associated with a 1-SD positive increase in dietary pattern score during period.

			Carb/fat balance pattern			Obesogenic pattern		
Timepoint	**Model**	**n**	**β**	**95%CI**	**p**	**β**	**95%CI**	**p**
0-6 months	*1*	280	-1.06	-1.66, -0.47	**<0.001**	0.62	0.14, 1.11	**0.013**
	1a	242	-1.22	-1.89, -0.55	**<0.001**	0.81	0.26, 1.35	**0.004**
	2	242	-1.22	-1.89, -0.55	**<0.001**	0.77	0.23, 1.31	**0.006**
	3	242	-1.18	-1.86, -0.51	**<0.001**	0.73	0.18, 1.29	**0.010**
6-12 months	*1*	229	-0.42	-0.88, 0.03	0.070	0.20	-0.20, 0.60	0.324
	1a	194	-0.28	-0.75, 0.20	0.248	0.12	-0.28, 0.53	0.547
	2	194	-0.34	-0.82, 0.13	0.158	0.20	-0.21, 0.62	0.341
	3	194	-0.21	-0.71, 0.29	0.417	0.06	-0.38, 0.50	0.782
0-12 months	*1*	255	-1.14	-1.85, -0.42	**0.002**	0.68	0.06, 1.30	**0.032**
	1a	214	-0.87	-1.65, -0.10	**0.028**	0.50	-0.17, 1.18	0.140
	2	214	-1.06	-1.83, -0.30	**0.007**	0.71	0.04, 1.38	**0.039**
	3	214	-0.98	-1.83, -0.14	**0.023**	0.60	-0.11, 1.32	0.098

1 – linear regression adjusted for start-of-period bodyweight and dietary pattern score in those with complete bodyweight, HbA1c and dietary pattern data during period.
1a – model 1 in sample restricted to those with complete covariate data.
2 – model 1a adjusted for age, sex, baseline under-reporting and change in total physical activity during period.
3 – model 2 adjusted for change in TEI during period (potential mediator between dietary pattern and bodyweight change).

Table S8.10: Relation between change in HbA1c (mmol/mol) and change in dietary pattern scores during study periods, with additional adjustment for trial arm in models 2-3.

β is the change in end-of-period HbA1c associated with a 1-SD positive increase in dietary pattern score during period.

			Carb/fat balance pattern			Obesogenic pattern		
Timepoint	**Model**	**n**	**β**	**95%CI**	**p**	**β**	**95%CI**	**p**
0-6 months	*1*	280	-2.16	-3.42, -0.91	**<0.001**	1.04	0.01, 2.07	**0.047**
	1a	242	-2.27	-3.69, -0.84	**0.002**	1.17	0.02, 2.33	**0.046**
	2	242	-1.88	-3.32, -0.44	**0.011**	0.80	-0.37, 1.96	0.179
	3	242	-1.38	-2.80, 0.05	0.058	0.48	-0.67, 1.64	0.408
6-12 months	*1*	229	-0.42	-1.47, 0.62	0.426	0.26	-0.66, 1.17	0.580
	1a	194	-0.25	-1.38, 0.88	0.663	0.09	-0.88, 1.06	0.854
	2	194	-0.38	-1.56, 0.80	0.530	0.11	-0.89, 1.11	0.831
	3	194	-0.54	-1.78, 0.71	0.397	0.23	-0.83, 1.29	0.672
0-12 months	*1*	256	-1.31	-2.34, -0.27	**0.014**	0.80	-0.09, 1.70	0.079
	1a	214	-0.68	-1.82, 0.46	0.240	0.48	-0.50, 1.46	0.335
	2	214	-0.82	-1.97, 0.33	0.159	0.58	-0.42, 1.58	0.254
	3	214	-0.76	-2.01, 0.49	0.231	0.50	-0.56, 1.55	0.353

1 – linear regression adjusted for start-of-period HbA1c and dietary pattern score in those with complete HbA1c and dietary pattern data during period.

1a – model 1 in sample restricted to those with complete covariate data.

2 – model 1a adjusted for trial arm, age, sex, baseline under-reporting, change in OHA medications (metformin, sulphonylurea and glitazones separately in percentages of maximum dose) and change in total physical activity during period.

3 – model 2 adjusted for change in TEI and bodyweight during period (potential mediators between dietary pattern and HbA1c change).

Figure S8.1*:* Dietary pattern factor loading diagrams.

Positive food group factor loadings increase dietary pattern scores, whilst negative loadings decrease dietary pattern scores. Highest and lowest loading food groups have the greatest impact on dietary pattern scores when changing intakes. *a*: 'Carb/fat balance' dietary pattern; *b*: 'Obesogenic' dietary pattern.

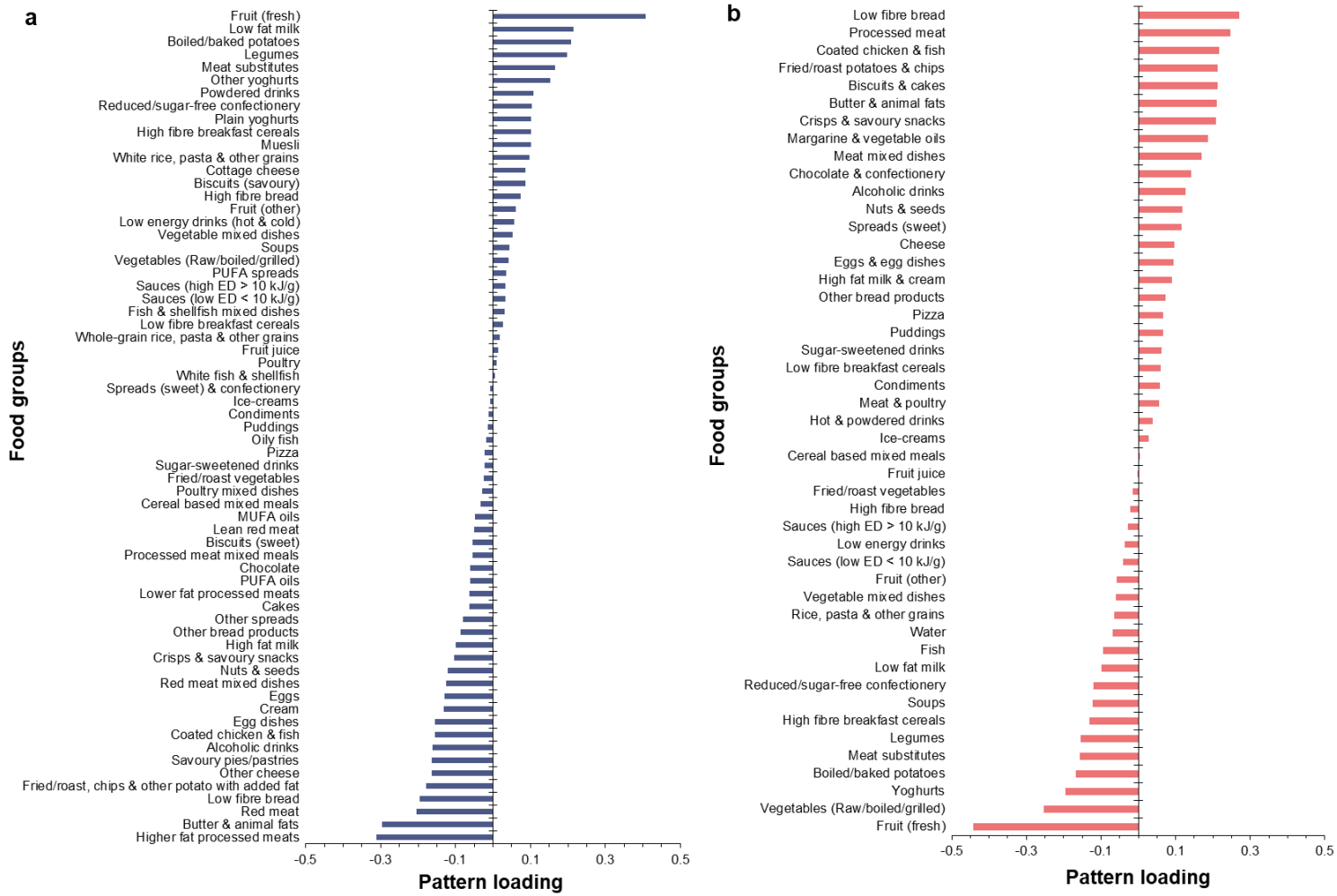
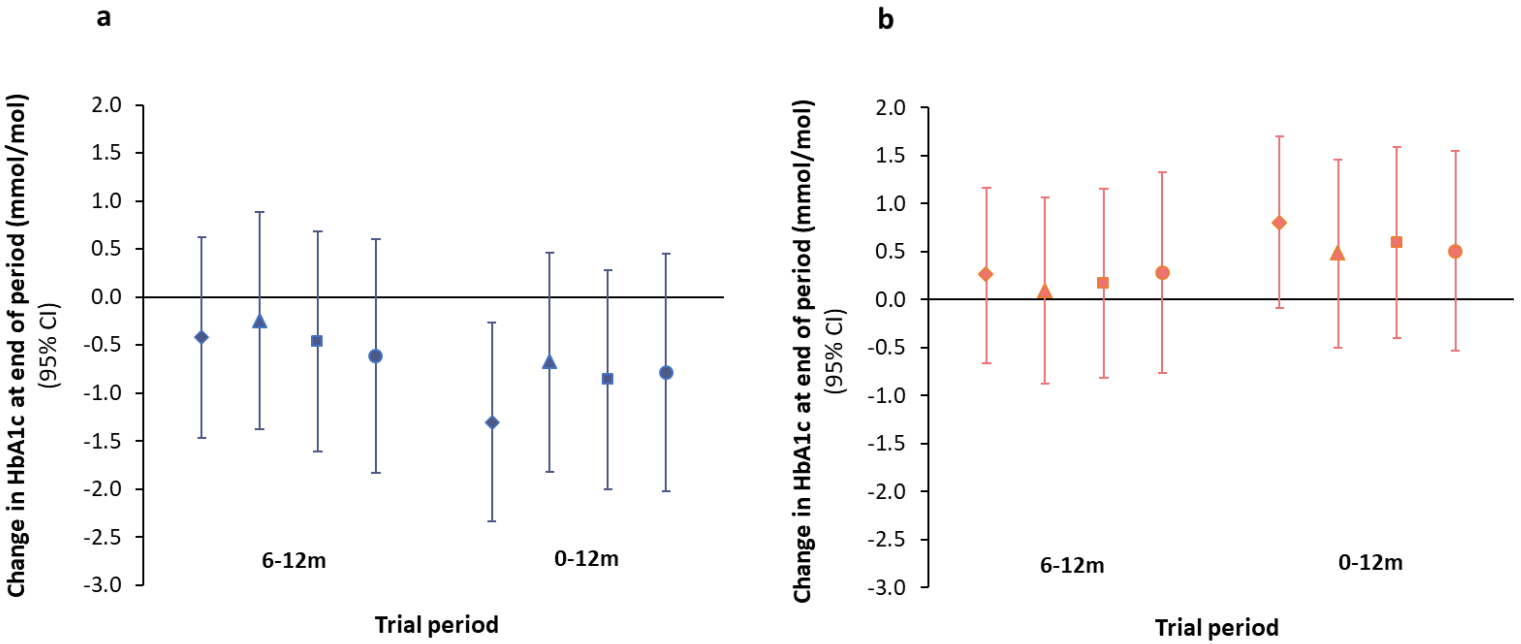


Figure S8.2*:* Associations between 1-SD increases in dietary pattern scores during 6-12 or 0-12 month periods and start-of-period-adjusted HbA1c at 12-months from multivariable linear regression.

Model 1a presents *Model 1* start-of-period dietary pattern score adjusted associations in those with complete covariate data. *Model 2* presents associations adjusted for potential confounders: age, sex, baseline under-reporting status, and change in total physical activity and percentage of maximum metformin, sulphonylurea and glitazone doses. *Model 3* presents Model 2 associations adjusted for potential mediators: change in bodyweight and energy intake. *a*: Associations between a 1-SD increase in 'carb/fat balance' dietary pattern score and end-of-period change in HbA1c; b: Associations between 1-SD increases in 'obesogenic' dietary pattern score and end-of-period change in HbA1c.



- ◆ **Model 1** - unadjusted (full sample): n=229 (6-12m), n=256 (0-12m)
- ▲ **Model 1a** - unadjusted (restricted sample): n=194 (6-12m), n=214 (0-12m)
- ■ **Model 2** - confounder adjusted: n=194 (6-12m), n=214 (0-12m)
- ● **Model 3** - mediator adjusted: n=194 (6-12m), n=214 (0-12m)

Figure S8.3*:* Fitted lines by sex from simple linear regression analyses of end-of-period HbA1c on 'carb/fat balance' and 'obesogenic' dietary pattern (DP) change, to investigate potential interactions between DP change and sex.

p_{int} – p-value for DP*sex interaction term calculated within model 2 (confounding-adjusted regression models). *a*: 6-month HbA1c on 0-6m 'carb/fat balance' DP change (p_{int}=0.98); *b*: 12-month HbA1c on 6-12m 'carb/fat balance' DP change (p_{int}=0.14); *c*: 12-month HbA1c on 0-12m 'carb/fat balance' DP change (p_{int}=0.12); *d*: 6-month HbA1c on 0-6m 'obesogenic' DP change (p_{int}=0.78); *e*: 12-month HbA1c on 6-12m 'obesogenic' DP change (p_{int}=0.23); *f*: 12-month HbA1c on 0-12m 'obesogenic' DP change (p_{int}=0.10).

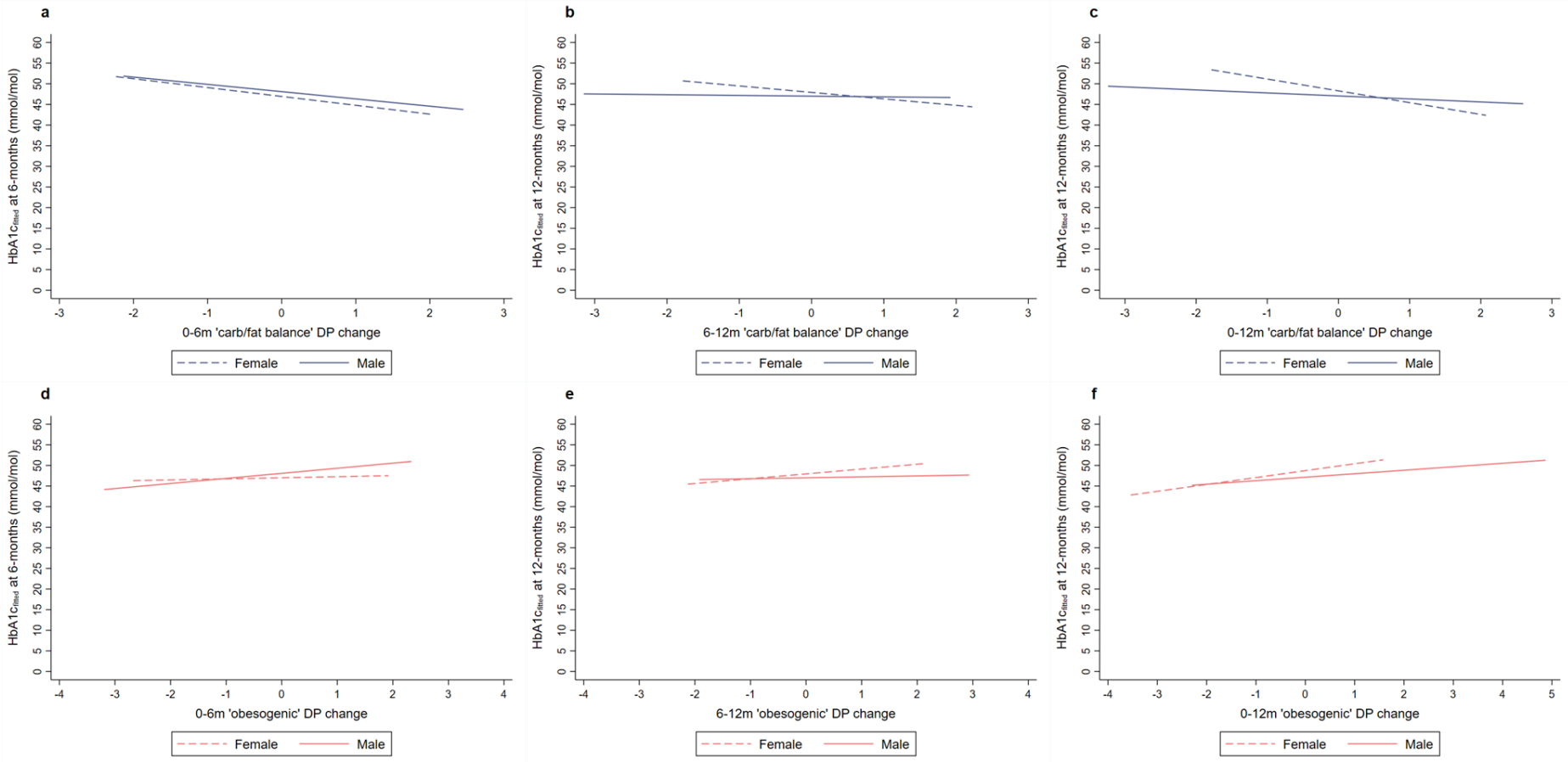
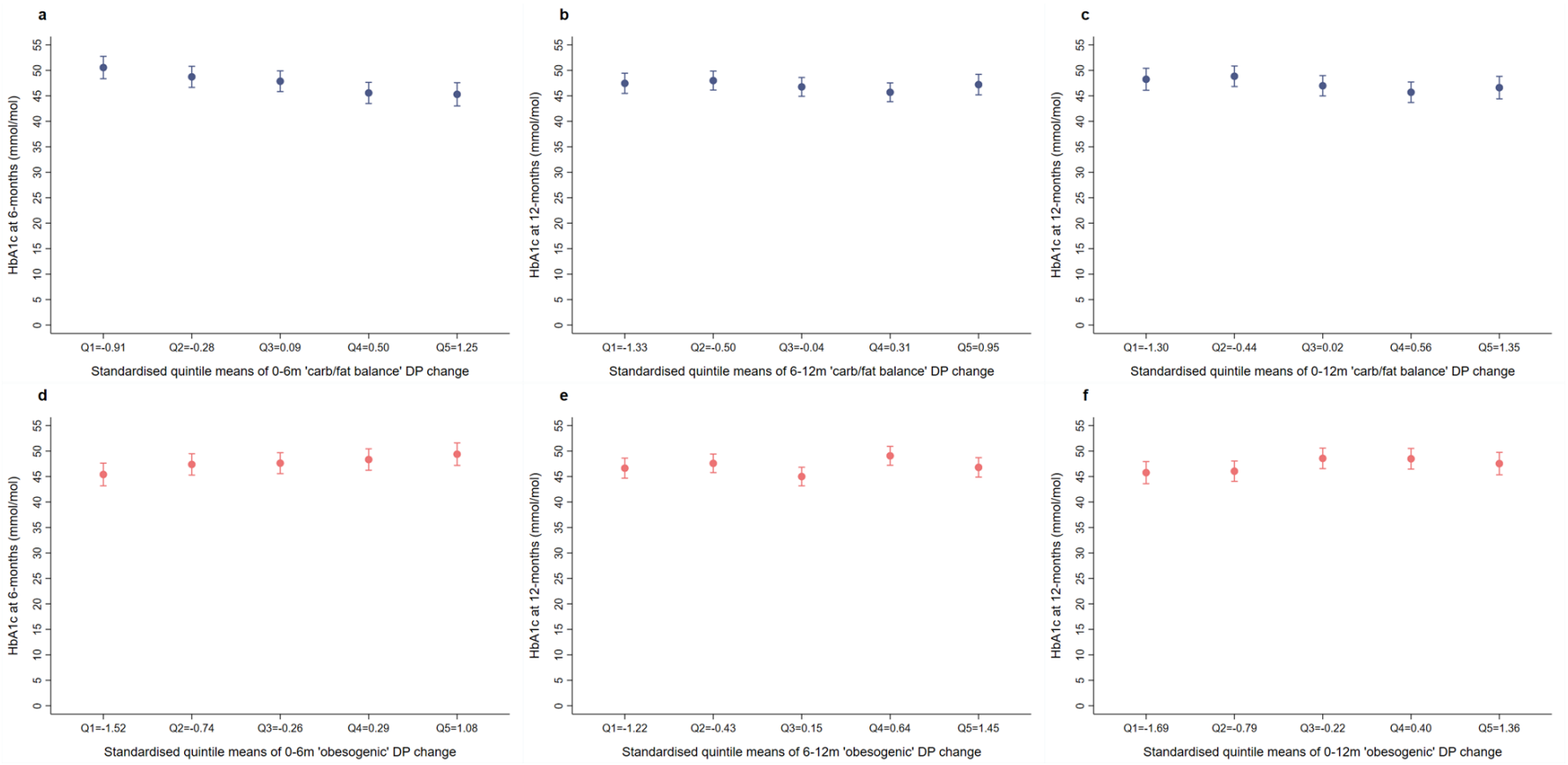


Figure S8.4: Linear trend assessment. Estimated marginal mean (95%CI) plots for HbA1c regressed on 'carb/fat balance' and 'obesogenic' dietary pattern (DP) score change quintiles for confounding-adjusted 0-6m, 6-12m and 0-12m period models (model 2).

p_{trend} – Model 2 linear test for trend performed using likelihood ratio test; modelling DP score change as a nested categorical (quintile) variable did not improve model fit compared to DP score change modelled as a continuous variable. Indications of a non-linear trend in panel *e* should be interpreted alongside the lack of evidence for non-linear trend in all other panels. *a*: 6-month HbA1c on 0-6m 'carb/fat balance' DP change quintiles (p_{trend}=0.27); *b*: 12-month HbA1c on 6-12m 'carb/fat balance' DP change quintiles (p_{trend}=0.40); *c*: 12-month HbA1c on 0-12m 'carb/fat balance' DP change quintiles (p_{trend}=0.31); *d*: 6-month HbA1c on 0-6m 'obesogenic' DP change quintiles (p_{trend}=0.41); *e*: 12-month HbA1c on 6-12m 'obesogenic' DP change quintiles (p_{trend}=0.02); *f*: 12-month HbA1c on 0-12m 'obesogenic' DP change quintiles (p_{trend}=0.18).



8.2 Supplementary Materials for Chapter 4 (Study 2)

Information S8.4: Random effect modelling

Trajectories for each dietary component were modelled with random intercepts but without random slopes. For the purposes of answering the research question in study 2, fixed effect estimates for the differences between groups (men and women) are required, rather than exploration of differences between each individual within these groups. Random intercepts are therefore necessary to account for average between-group differences between men and women, but not within-group differences in trajectories. Models with random intercepts but fixed slopes imply constant mean differences within, in this case, sexes over time (specifically, how diet trajectories for each sex differ from the sample average trajectory). This is suited to answering whether men and women differ as groups and analysis power will also be maximized given there are less parameters (i.e. for random slope variances) to be calculated from the available data.

Information S8.5: Multilevel models do not require complete data across time

Within multilevel models, residuals for individuals with fewer datapoints will be 'shrunken', meaning they do offer information on diets at the timepoints measured but may not impart information for all period trajectories (if only 1 dietary measure available, then such participants will impart no information on trajectories) [381]. Predicted trajectories in the sample will be pulled towards the means of those who have more data. There is thus no need to drop participants in such models, maximising sample size/power.

Information S8.6: Suppression mediation by energy under-reporting status and glucose-lowering medication differences between men and women.

Although a consistent factor associated with dietary under-reporting is higher BMI [445], evidence has been inconsistent for energy under-reporting differing between men and women. A recent meta-analysis of 31 validation studies comparing sex differences in self-reported energy intake to doubly labelled water (DLW)-assessed energy expenditure, found that women under-reported absolute energy intakes to a lesser extent than men when diets were assessed via food records [446]. This also appeared to be the case within the Early-ACTID cohort (Table 4.1). However, McKenzie et al [446] found that any sex differences in misreporting disappeared when comparing

reported intakes as percentage-estimated total energy, and no sex differences in misreporting were found for other self-report methods.

A separate systematic review including 32 such validation studies containing both men and women (18 of which were common to the systematic review by McKenzie et al. [446]) found that under-reporting was inconsistent between studies but seemingly more common in women, varying in degree by type of dietary measure [447], and in line with previous reviews [448]. Studies where weight loss occurred were however included in the review by Burrows et al, potentially biasing conclusions given misreporting status is based on assuming energy balance between total energy expenditure and reported energy intake. Due to the possibility that sex differences do exist in the prevalence of dietary misreporting, misreporting status in Early-ACTID and its follow-up was explored as a potential suppression mediator between sex and dietary pattern trajectories (Model 1a).

For suppression mediation to be occurring, associations between predictor and mediator (e.g. sex and under-reporting status) would be the opposite sign to the association between mediator and outcome (under-reporting status and dietary pattern scores) i.e. women who under-report energy intake more may also report lower dietary pattern scores (as might be expected with an energy-dense, higher-fat, lower-fibre 'obesogenic' dietary pattern). In this case, there would be no evidence of association observed between sex and dietary pattern change without adjustment for under-reporting status.

Similarly, women may be on higher doses of appetite-affective medications compared to men and higher appetite-affective medication doses may also associate with lower dietary pattern scores through reducing intakes. Adjustment for glucose-lowering medications may therefore also reveal evidence of suppression mediation. There is currently little research into whether there exists sex-differences in glucose-lowering medication use in type 2 diabetes. However, sex-differences have been shown to exist in the prescription of CVD-related medications in type 2 diabetes. Women in England were found to be prescribed less lipid-lowering and blood pressure medications compared to men, even where clinically indicated [449]. Glucose-lowering medications were thus assessed as a potential suppression mediator between sex and dietary pattern trajectories within sensitivity analyses (Model 1b).

Table S8.11: Number of participants on diabetes medications in those with diet data at any timepoint, n (%).

Glitazone medications were not incorporated into either the 'appetite-affective' or 'hypo-affective' medication grouping, as although associated with weight gain, it remains unclear whether this is due to induced fluid retention rather than increased adiposity [380]. Additionally, glitazone use has not been associated with inducing hypoglycaemic attacks [380].

	Timepoint				
	0m	**6m**	**1y**	**3y**	**6y**
Medication data available	331 (100%)	331 (100%)	331 (100%)	286 (86%)	269 (81%)
Metformin	116 (35%)	119 (36%)	130 (39%)	138 (48%)	170 (63%)
Sulphonylurea	29 (9%)	31 (9%)	30 (9%)	45 (16%)	55 (21%)
Glitazone	3 (1%)	4 (1%)	4 (1%)	10 (3%)	10 (4%)
Acarbose	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)
DPP-4	0 (0%)	0 (0%)	0 (0%)	2 (1%)	19 (7%)
GLP-1	0 (0%)	0 (0%)	0 (0%)	3 (1%)	13 (5%)
Insulin	0 (0%)	0 (0%)	1 (0%)	6 (2%)	12 (4%)

Table S8.12**:** Variation in measurement times in relation to trial protocols.

Within Models 1-5, to account for variation in exact measurement times between individuals, time has been modelled as a continuous variable rather than its trial protocol-rounded values.

Measurement Time in months *(per protocol)*	**Measurement Time in months** *(actual)*			
	Mean (SD)	**Median (Q1, Q3)**	**Min**	**Max**
0	0.0 (0.0)	0.0 (0.0, 0.0)	0.0	0.0
6	7.0 (1.0)	6.9 (6.4, 7.4)	2.1	9.7
12	12.9 (0.8)	12.8 (12.4, 13.3)	7.7	17.0
36	37.5 (1.7)	37.2 (36.5, 38.3)	31.7	43.0
72	73.2 (1.9)	72.9 (72.2, 74.1)	61.9	83.7

Q1 – quartile 1; Q3 – quartile 3

Table S8.13: Baseline characteristics of all Early-ACTID intervention participants and of analysis sample for assessing potential sample selection bias.

		Early-ACTID	**Analysis sample**
N		494	331
n (%)			
	Female	173 (35%)	117 (35%)
	Male	321 (65%)	214 (65%)
Age (years)		61 (53, 68)	62 (56, 68)
Total physical activity (cpm)		286 (221, 362)	286 (221, 362)
MVPA (mins/day)		21 (11, 35)	20 (11, 35)
IMD score		13.2 (7.1, 20.6)	12.8 (7.2, 19.7)
Weight (kg)		88.7 (79.3, 98.6)	87.0 (77.1, 96.6)
Weight change 0-6 months (kg)		-1.7 (-3.7, 0.2)	-2.0 (-3.8, 0.0)
BMI (kg/m^2)		30.1 (27.7, 34.2)	29.6 (27.3, 33.1)
On appetite-affective medications (n(%))		174 (35%)	116 (35%)
Appetite-affective medications (%max dose)		0 (0, 33)	0 (0, 33)
On 'hypo'-affective medications (n(%))		43 (9%)	29 (9%)
'Hypo'-affective medications (%max dose)		0 (0, 0)	0 (0, 0)

Data presented as median (Q1, Q3) or n(%).

Table S8.14: Missing dietary data patterns in participants included within analyses sample (Models 1-5).

Dietary data missingness indicator 1 assigned for sustained study attrition from the 12-month or 3-year timepoints. Missingness pattern indicator 2 assigned to all other missingness patterns not explained by missingness indicator 1.

Dietary data missingness pattern [a] (+ = available; . = missing)	**Number of missing values**	**Frequency**	**Missingness pattern indicator assigned**
+++++	0	103	-
+++..	2	101	1
..+..	4	29	1
+++.+	1	29	2
++...	3	25	1
+....	4	13	1
+.+..	3	13	1
++.++	1	13	2
++..+	2	11	2
+.+++	1	11	2
..+.+	3	8	2
....+	4	7	2
..+++	2	7	2
.+..+	3	2	2
+.+.+	2	2	2
+..++	2	2	2
.+...	4	1	1
+...+	3	1	2
.+.++	2	1	2

[a] *Missing data patterns in order of time: 0-, 6, 12-months, 3-, 6-years*

Table S8.15: Associations between dietary data missingness pattern indicators and Model 1 exposure (sex) and outcome (dietary pattern scores) obtained via simple logistic regression.

Dietary data missingness patterns were not associated with main analysis model exposure or outcome. Main analysis models thus needed no further adjustment for predictor/proxy variables, which may have associated with dietary data missingness patterns, as these patterns do not appear to be confounding associations between Model 1 exposure and outcome. β's and their 95%CI are presented as log odds ratios.

		Missingness pattern indicator 1			**Missingness pattern indicator 2**		
N	**Exposure Variable**	**β**	**95%CI**	**p**	**β**	**95%CI**	**p**
285	Obesogenic dietary pattern score 0m	0.07	-0.17, 0.31	0.547	-0.27	-0.86, 0.32	0.366
266	Obesogenic dietary pattern score 6m	-0.01	-0.27, 0.24	0.928	-0.15	-0.73, 0.43	0.617
268	Obesogenic dietary pattern score 12m	-0.06	-0.30, 0.18	0.618	0.15	-0.43, 0.73	0.612
127	Obesogenic dietary pattern score 3y	-	-	-	0.12	-0.51, 0.75	0.708
178	Obesogenic dietary pattern score 6y	-	-	-	0.10	-0.26, 0.45	0.604
331	Sex	-0.37	-0.82, 0.08	0.111	-0.53	-1.27, 0.20	0.155

Table S8.16: Estimates for changes in dietary pattern scores during each period of study in men and women, and their difference, after adjusting for 1a) potential suppression mediation by energy under-reporting status, 1b) potential suppression mediation by glucose-lowering medication use, and 1c) trial arm, to assess for potential change differences due to intervention received (diet only or diet with physical activity).

β's and 95%CI represent change in dietary pattern score per 6-months period; changes presented for 0-6m and 6-12m can therefore be considered to represent total change during these periods. Unadjusted Model 1 estimates are shown for ease of comparison of model estimates.

			Male		Female		Difference (Female – Male)		
Model	**N**	**Dietary pattern change**	**β**	**95%CI**	**β**	**95%CI**	**β**	**95%CI**	**p_{diff}**
1	331	Dietary pattern change 0-6m (SD/6-months)	-0.26	-0.40, -0.12	-0.16	-0.35, 0.04	0.10	-0.13, 0.34	0.393
		Dietary pattern change 6-12m (SD/6-months)	0.18	0.01, 0.35	-0.06	-0.30, 0.18	-0.24	-0.53, 0.06	0.114
		Dietary pattern change 1-6y (SD/6-months)	0.01	0.00, 0.03	0.03	0.01, 0.06	0.02	-0.01, 0.05	0.183
1a	285	Dietary pattern change 0-6m (SD/6-months)	-0.30	-0.50, -0.10	-0.18	-0.41, 0.05	0.12	-0.13, 0.36	0.348
		Dietary pattern change 6-12m (SD/6-months)	0.20	-0.05, 0.44	-0.06	-0.36, 0.23	-0.26	-0.56, 0.05	0.097
		Dietary pattern change 1-6y (SD/6-months)	0.00	-0.02, 0.03	0.03	-0.01, 0.06	0.02	-0.01, 0.06	0.165
1b	331	Dietary pattern change 0-6m (SD/6-months)	-0.30	-0.47, -0.12	-0.15	-0.37, 0.07	0.15	-0.09, 0.38	0.229
		Dietary pattern change 6-12m (SD/6-months)	0.19	-0.02, 0.40	-0.05	-0.33, 0.22	-0.24	-0.54, 0.05	0.102
		Dietary pattern change 1-6y (SD/6-months)	0.01	-0.02, 0.03	0.03	-0.01, 0.06	0.02	-0.01, 0.05	0.251
1c	331	Dietary pattern change 0-6m (SD/6-months)	-0.24	-0.42, -0.05	-0.14	-0.35, 0.08	0.10	-0.14, 0.34	0.414
		Dietary pattern change 6-12m (SD/6-months)	0.10	-0.13, 0.32	-0.13	-0.40, 0.14	-0.22	-0.52, 0.07	0.137
		Dietary pattern change 1-6y (SD/6-months)	0.01	-0.01, 0.04	0.03	0.00, 0.06	0.02	-0.01, 0.05	0.190

Table S8.17: Congruence coefficients [342] between 'obesogenic' dietary patterns derived at baseline (0m) and dietary patterns derived at all other timepoints for demonstrating pattern structural similarity between timepoints.

A congruence coefficient between dietary patterns at separate timepoints of ≥0.95, 0.85-0.94, or <0.85 suggest good, fair, or unacceptable similarity respectively [342]. Congruence was classed as 'fair' between 0m and all other timepoints except at 3-years. Scoring intakes at each timepoint relative to the 0m dietary pattern structure thus captures sufficient variation in diet at each timepoint but less so at 3 years. However, projecting this single, 0-month dietary pattern structure onto other timepoint data allows for a meaningful analysis of changes in a single dietary pattern score over time.

Pattern comparison	Congruence coefficient	Congruence
0m - 6m	0.90	fair
0m – 12m	0.90	fair
0m - 3yrs	0.81	poor
0m - 6yrs	0.90	fair

Table S8.18: Explained nutrient variation and nutrient correlations for energy-dense, higher-fat, lower-fibre 'obesogenic' dietary patterns derived independently at 0-, 6-, 12-months, 3- and 6-years.

	Explained variation (%)					Correlation coefficient		
Timepoint	Nutrient intakes (total)	DED (g/kJ)	Fat (%)	Fibre density (g/MJ)	Food intake (total)	DED (g/kJ)	Fat (%)	Fibre density (g/MJ)
0 months	51.3	66.7	35.9	51.2	3.4	0.81	0.60	-0.72
6 months	58.1	73.3	44.4	56.5	3.6	0.86	0.67	-0.75
12 months	58.1	70.4	47.0	56.9	3.8	0.84	0.69	-0.75
3 years	56.4	67.4	42.5	59.3	4.5	0.82	0.65	-0.77
6 years	51.1	67.8	33.3	52.3	3.7	0.82	0.58	-0.72

DED – dietary energy density.

Table S8.19: Congruence coefficients between dietary patterns derived at baseline (0m) and dietary patterns derived independently at all other timepoints, for dietary patterns derived only in those participants with data available at 3-years.

Pattern structural similarity between 0-12m and 0m-6yrs timepoints changes from fair (Table S8.17) to poor when restricted to those participants with data available at 3 years. Only congruence between 0m and 6m remains fair although congruence is reduced. The poor dietary pattern congruence between 0m-3yrs observable in Table S8.17 could thus be a results of the lower sample size available for dietary pattern analysis at 3 years (N=127).

Pattern comparison	Congruence coefficient	Congruence
0m - 6m	0.86	fair
0m - 12m	0.79	poor
0m - 3yrs	0.78	poor
0m - 6yrs	0.82	poor

Table S8.20: Food group factor loadings for energy-dense, high-fat, low-fibre 'obesogenic' dietary patterns derived independently in men and in women at Early-ACTID baseline.

	Food group factor loading	
Food Group	**Men**	**Women**
Fruit (fresh)	-0.435	-0.421
Vegetables (Raw/boiled/grilled)	-0.278	-0.168
Boiled/baked potatoes	-0.213	-0.087
Yoghurts	-0.213	-0.142
Legumes	-0.159	-0.166
High fibre breakfast cereals	-0.131	-0.188
Soups	-0.127	-0.111
Low fat milk	-0.123	-0.027
Meat substitutes	-0.118	-0.188
Sauces (high ED > 10 kJ/g)	-0.082	0.056
Rice, pasta & other grains	-0.076	-0.046
Vegetable mixed dishes	-0.073	-0.054
Fish	-0.070	-0.135
Water	-0.061	-0.035
Fruit juice	-0.055	0.058
High fibre bread	-0.046	0.033
Reduced/sugar-free confectionery	-0.035	-0.214
Sauces (low ED < 10 kJ/g)	-0.031	-0.043
Fruit (other)	-0.029	-0.064
Low energy drinks	-0.008	-0.044
Meat & poultry	-0.006	0.159
Low fibre breakfast cereals	-0.002	0.149
Fried/roast vegetables	0.001	-0.065
Pizza	0.016	0.135
Hot & powdered drinks	0.021	0.097
Sugar-sweetened drinks	0.024	0.116
Ice-creams	0.035	0.020
Other bread products	0.055	0.112
Puddings	0.056	0.066
Cereal based mixed meals	0.058	-0.073
Condiments	0.069	-0.005
High fat milk & cream	0.079	0.104
Cheese	0.091	0.123
Alcoholic drinks	0.100	0.059
Eggs & egg dishes	0.106	0.056
Nuts & seeds	0.126	0.099
Spreads (sweet)	0.139	0.068
Margarine & vegetable oils	0.142	0.221
Meat mixed dishes	0.179	0.140
Chocolate & confectionery	0.183	0.134
Butter & animal fats	0.209	0.203
Processed meat	0.218	0.226
Biscuits & cakes	0.219	0.254
Low fibre bread	0.220	0.305
Fried/roast potatoes & chips	0.223	0.180
Crisps & savoury snacks	0.223	0.178
Coated chicken & fish	0.244	0.089

Figure S8.5: Model 1 (outcome: dietary pattern scores) residual diagnostics.

a – Histogram of overall model residuals to assess assumptions of level-1 residual normality; b - Histogram of model intercept residuals to assess assumptions of level-2 residual normality; c - Overall model residuals plotted against time to assess assumptions of homoscedasticity of model residuals over time; d - Overall model residuals plotted against model-predicted outcome values to assess assumptions of residual independence from predicted values.

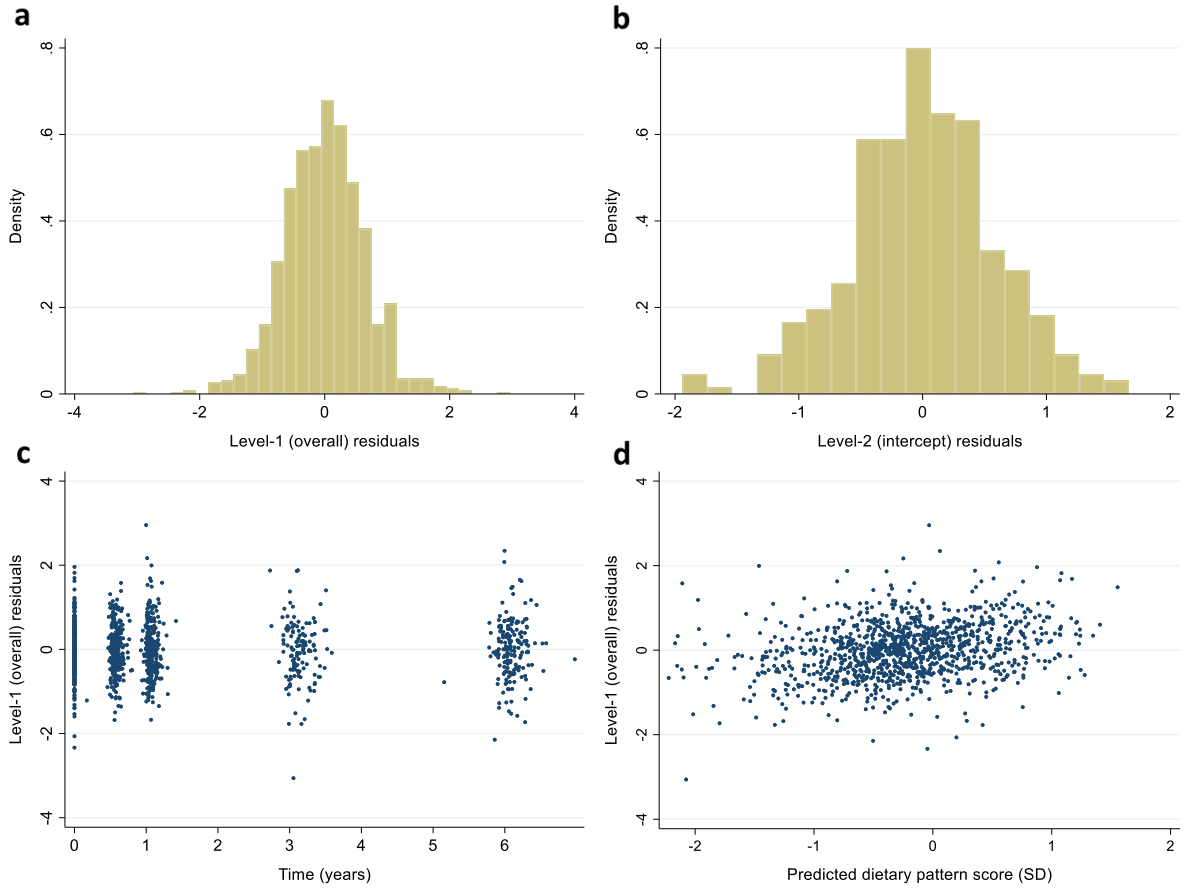


Figure S8.6: Model 2a (outcome: raw energy intakes) residual diagnostics.

a – Histogram of overall model residuals to assess assumptions of level-1 residual normality; b - Histogram of model intercept residuals to assess assumptions of level-2 residual normality; c - Overall model residuals plotted against time to assess assumptions of homoscedasticity of model residuals over time; d - Overall model residuals plotted against model-predicted outcome values to assess assumptions of residual independence from predicted values.

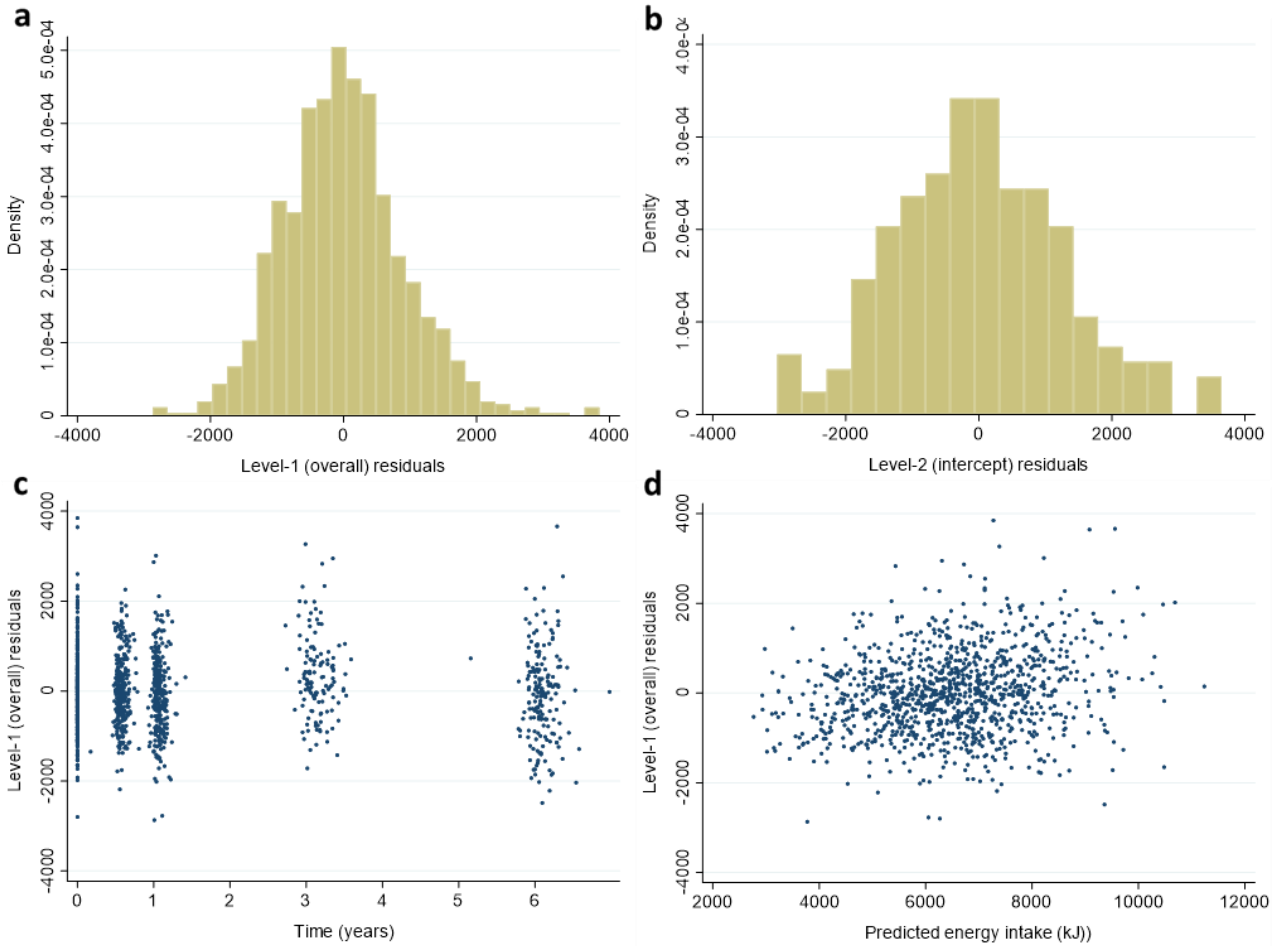


Figure S8.7: Model 2b (outcome: energy as percentage of baseline intakes) residual diagnostics.

a – Histogram of overall model residuals to assess assumptions of level-1 residual normality; b - Histogram of model intercept residuals to assess assumptions of level-2 residual normality; c - Overall model residuals plotted against time to assess assumptions of homoscedasticity of model residuals over time; d - Overall model residuals plotted against model-predicted outcome values to assess assumptions of residual independence from predicted values; percentage energy intakes relative to baseline at baseline were constrained to 100% for each participant and hence produced heteroskedastic residuals over predicted outcome values (see also Figure S8.8).

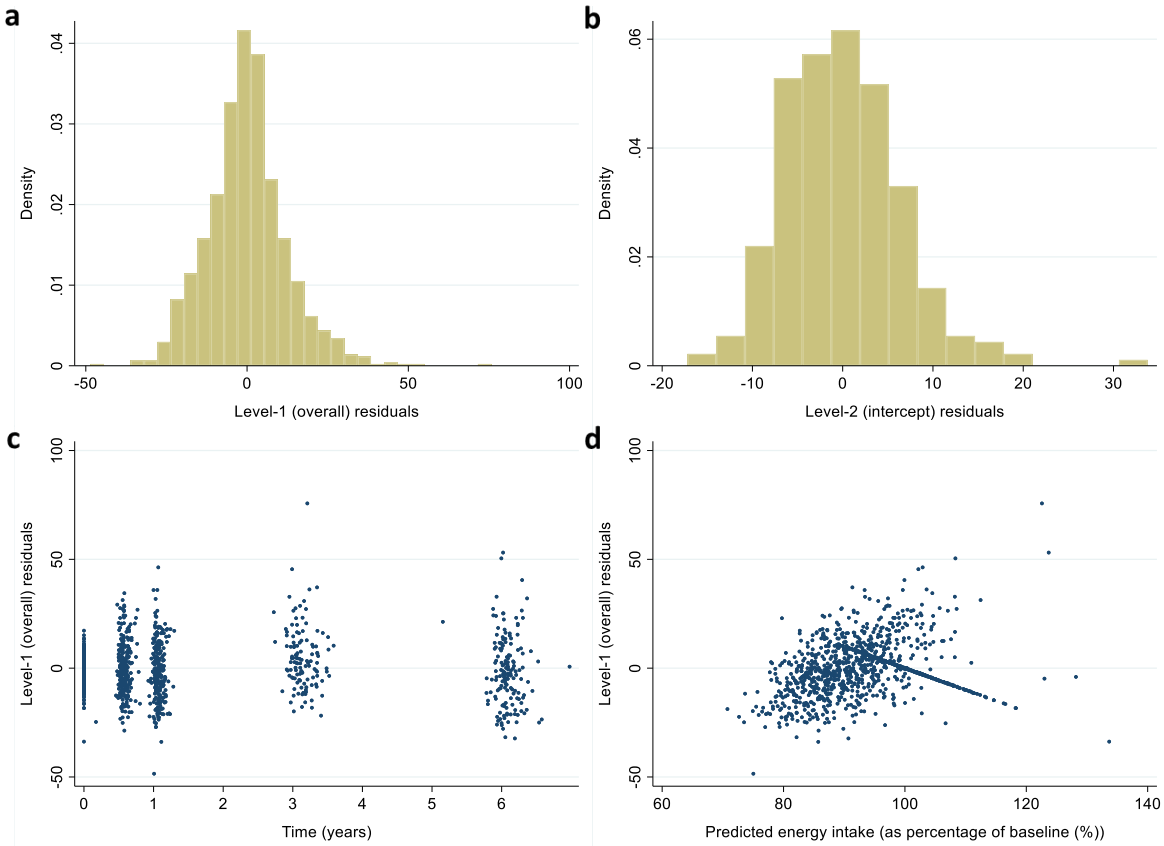


Figure S8.8: Model2b (outcome: energy as percentage of baseline intakes) residual diagnostics repeated separately in men and women.

Residual trends can be seen to be equal between sexes and subsequent trend comparisons of percentage energy change from baseline over time between sexes can be considered appropriate within Model 2b. Histogram of overall model residuals to assess assumptions of level-1 residual normality in women (a) and men (e); Histogram of model intercept residuals to assess assumptions of level-2 residual normality in women (b) and men (f); Overall model residuals plotted against time to assess assumptions of homoscedasticity of model residuals over time in women (c) and men (g); Overall model residuals plotted against model-predicted outcome values to assess assumptions of residual independence from predicted values in women (d) and men (h).

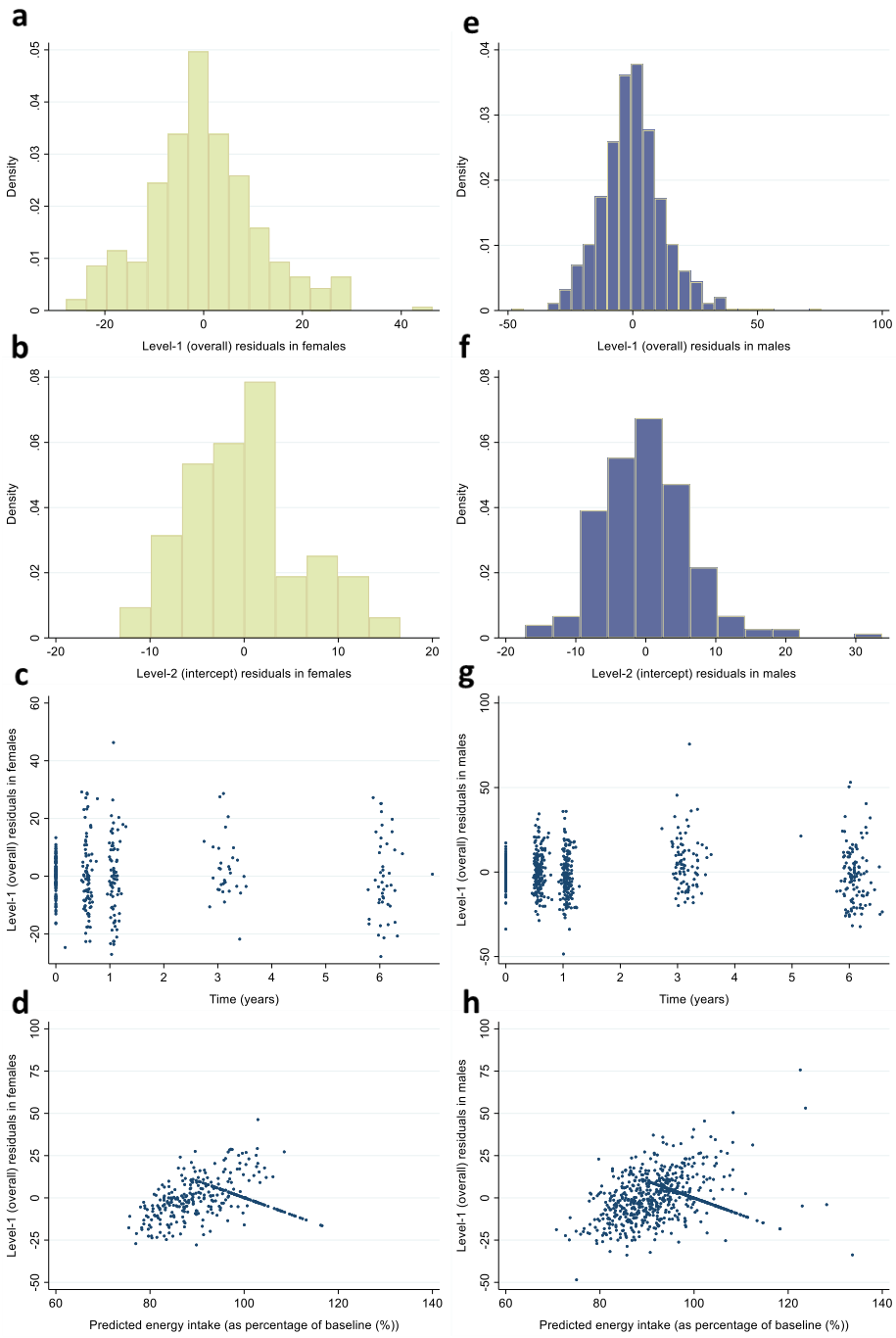


Figure S8.9: Model 3 (outcome: energy density) residual diagnostics.

a – Histogram of overall model residuals to assess assumptions of level-1 residual normality; b - Histogram of model intercept residuals to assess assumptions of level-2 residual normality; c - Overall model residuals plotted against time to assess assumptions of homoscedasticity of model residuals over time; d - Overall model residuals plotted against model-predicted outcome values to assess assumptions of residual independence from predicted values.

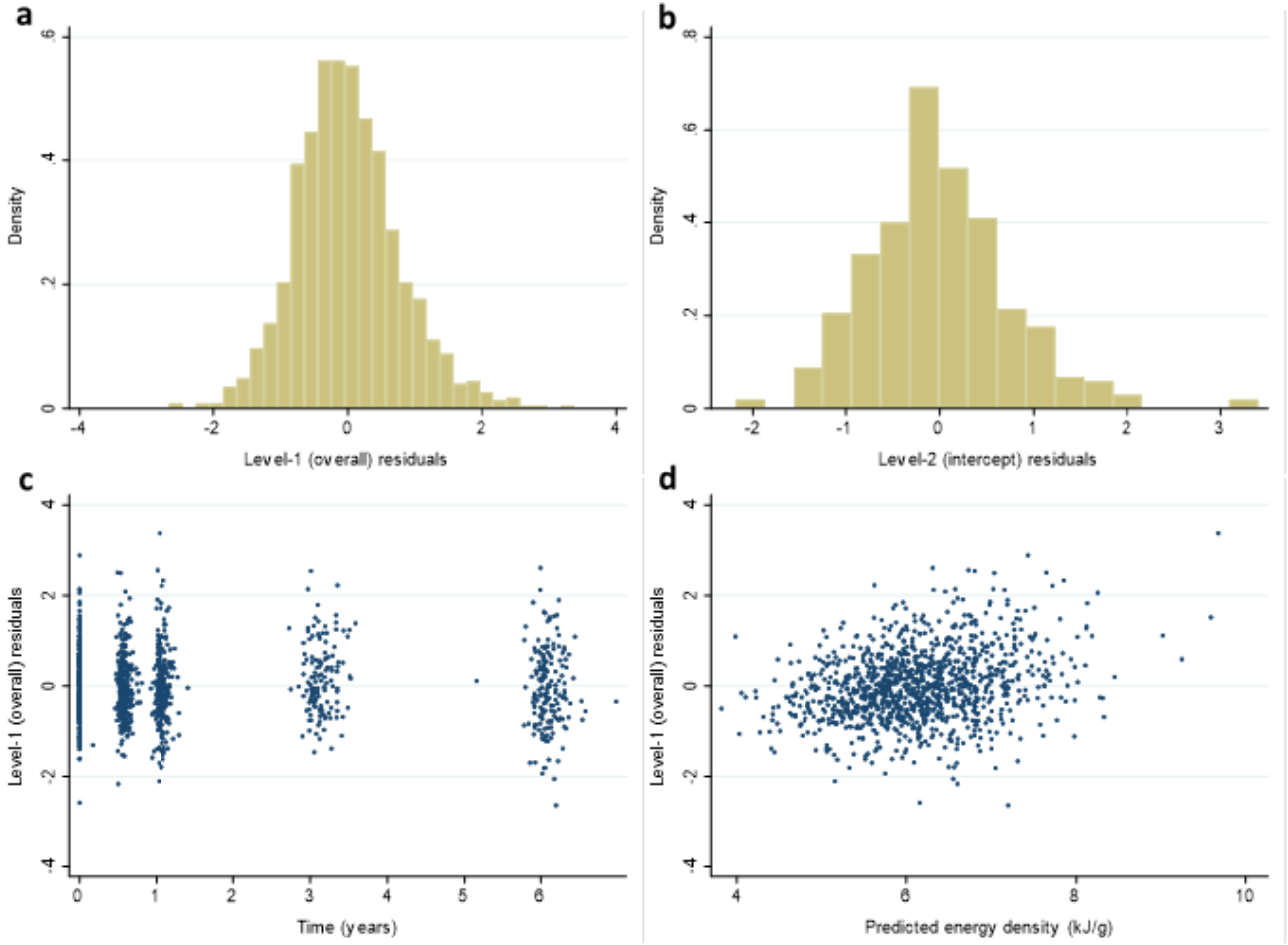


Figure S8.10: Model 4 (outcome: Percentage energy from fat) residual diagnostics.

a – Histogram of overall model residuals to assess assumptions of level-1 residual normality; b - Histogram of model intercept residuals to assess assumptions of level-2 residual normality; c - Overall model residuals plotted against time to assess assumptions of homoscedasticity of model residuals over time; d - Overall model residuals plotted against model-predicted outcome values to assess assumptions of residual independence from predicted values.

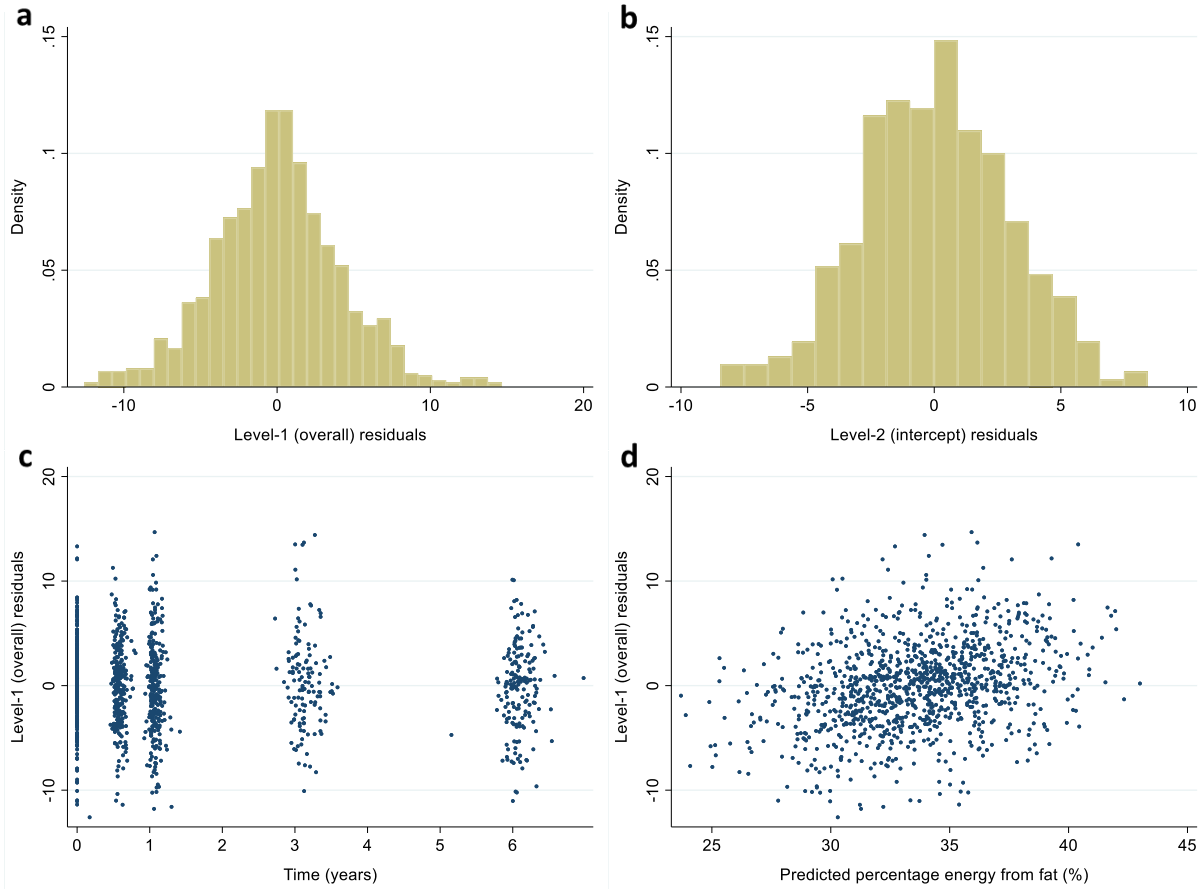


Figure S8.11: Model 5 (outcome: fibre density) residual diagnostics.

a – Histogram of overall model residuals to assess assumptions of level-1 residual normality; b - Histogram of model intercept residuals to assess assumptions of level-2 residual normality; c - Overall model residuals plotted against time to assess assumptions of homoscedasticity of model residuals over time; d - Overall model residuals plotted against model-predicted outcome values to assess assumptions of residual independence from predicted values.

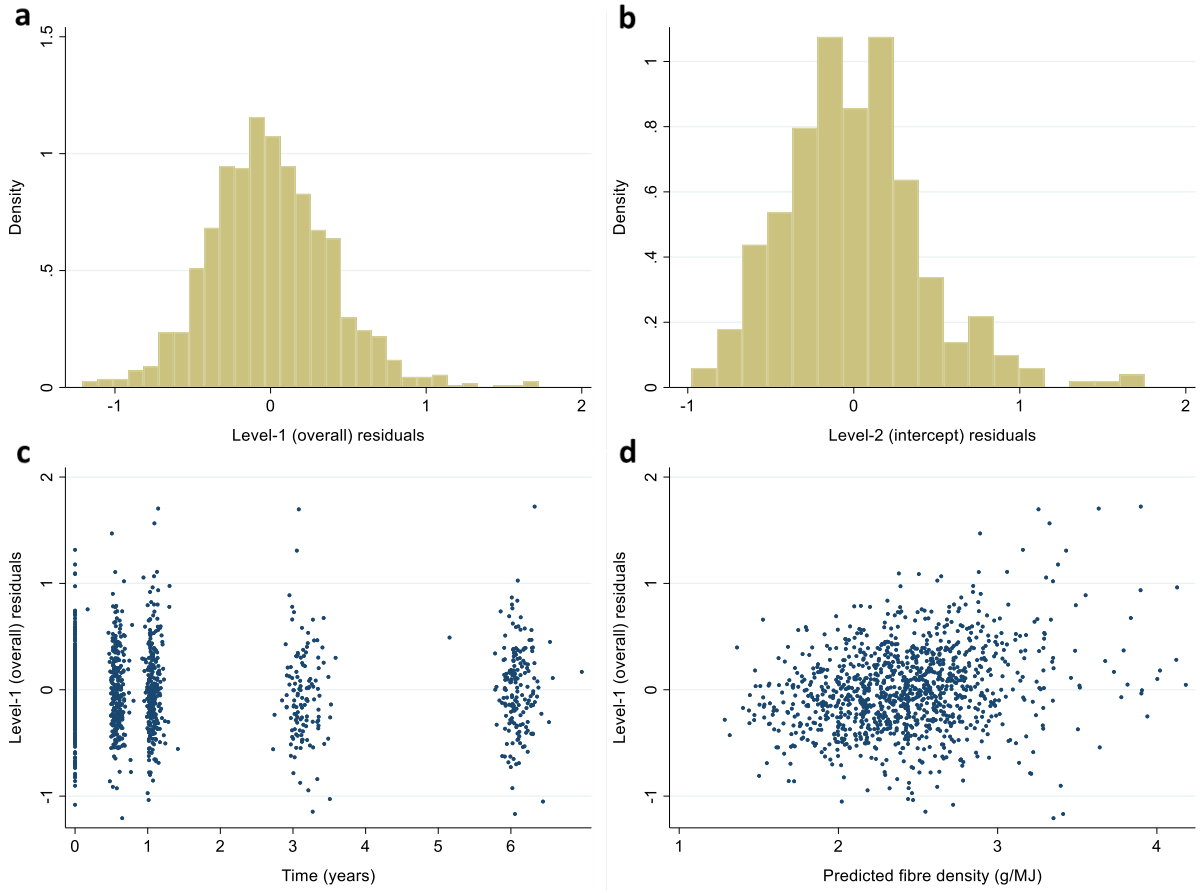


Figure S8.12: 'Obesogenic' dietary pattern factor loadings from running RRR independently at baseline (N=285) and 3-years (N=127); Coefficient of Congruence (CC) <0.85 (Table S8.17).

Other timepoint factor loadings are not shown due to similarity with baseline (CC>0.85). Positive food group factor loadings increase dietary pattern scores, whilst negative loadings decrease dietary pattern scores. For practicality, dietary pattern factor loadings from baseline were used to score intakes at all other timepoints within Model 1 to measure adherence to the same score over time.

8.3 Supplementary Materials for Chapter 5 (Study 3)

Information S8.7: Longitudinal and Random effects modelling

In multilevel models, residuals for individuals with fewer datapoints will be 'shrunken', meaning information on HbA1c is included at the timepoints measured but may not impart information for all period trajectories (e.g. if only 1 HbA1c measure is available for a participant, then such participants will impart no information on HbA1c trajectories) [381]. Predicted trajectories in the sample will be pulled towards the means of those who provide more data. As multilevel models do not require complete data across time, there is thus no need to drop participants from such models, maximizing overall sample size/power.

Each potentially time-varying main model predictor was assessed for whether changes over time were deemed significant enough to require modelling longitudinally (rather than adjusting for only baseline values). This was done by calculating the Intraclass Correlation Coefficient (ICC) from a linear/logistic empty means, random intercept model, with no exposures and with the repeatedly measured predictor as the outcome. The ICC ranges from 0 to 1 and demonstrates how much a variable varies between- or within-persons, with a value equal to unity indicating that all variation in the predictor is between-persons and none within-persons (does not change/is stable over time). The ICC for under-reporting status, for example, was equal to 0.98 (Information S8.7 Table 1), meaning 98% of variation in under-reporting status was between-person and only 2% was within-persons. Baseline under-reporting status was therefore included in models 2-3 only. This maximises the available power for finding associations between dietary patterns and HbA1c change, and adds further weight to the assumption that misreporting status can be assumed to track within-individuals over time [346]. All predictors shown in Information S8.7 Table 1 were modelled as time-varying except for under-reporting status.

Trajectories for HbA1c (main outcome) were modelled in a multilevel framework with both random intercepts and slopes. For the purposes of answering the research question, models must be able to explore differences between each individual. Random intercepts are necessary to account for between-person mean differences in HbA1c, and random slopes for accounting for within-person differences from group-mean HbA1c change slopes over time. Models with both random intercepts and slopes thus allow mean differences between individuals to vary over time.

Each time-varying predictor (dietary pattern score, energy intake, glucose-lowering medications and bodyweight) were assessed for whether longitudinal change was best described with a fixed or

random trajectory. This was done by comparing Aikake Information Criterion (AIC) and Bayesian Information Criterion (BIC) values between a series of multilevel models run with either a random intercept or random slope, with each main model predictor (dietary pattern score, energy intake, glucose-lowering medications or bodyweight) as outcome and with time as the only exposure [381]. Lower AIC/BIC values indicate a more parsimonious model fit and inform on whether these main model predictors would be best described with fixed or randomly-varying trajectories. However, given limitations in Stata software to model variables with random trajectories in addition to modelling random trajectories for the main model outcome, all predictor variables within main model 1-3 were modelled with fixed slopes only. Assessment of AIC/BIC values thus helped determine whether model 1-3 estimates for predictors that do randomly-vary over time are potentially biased or not.

Modelling random trajectories for dietary pattern scores (the main model exposure) was not indicated to improve model fit (Information S8.7 Table 2) and thus modelling fixed slopes in disaggregated between/within-person form can be assumed not to introduce bias into their estimates. However, estimates for time-varying predictors that do appear to follow randomly-varying trajectories (that is, glucose-lowering medications and bodyweight) should not be interpreted directly within models 1-3 as disaggregation into between- and within-person effects for such variables will be 'incomplete', hence providing potentially biased estimates for these specific variables [381]. This is because variation within these predictor variables will be dependent on time, and therefore, their effect estimates and calculated level of significance will differ depending on which reference timepoint is used for time zero (baseline for models 1-3) [381]. However, glucose-lowering medications and bodyweight are not the main exposures of interest in this study and should still be included in models 1-3 to account for their potential confounding/mediation of dietary pattern and HbA1c associations.

Information S8.7 Table 1: Intra-class correlation coefficients (ICC) for main model 2-3 predictors which are measured repeatedly over time, calculated from linear/logistic empty means, random intercept models, with each variable as independent outcomes. Repeated measures of total physical activity were not assessed in this way as there was insufficient data at later timepoints with which to model longitudinally.

Predictor	Model type (multilevel)	ICC
Dietary pattern score	linear	0.43
Energy intake	linear	0.62
Under-reporting status	logistic	0.98
Metformin dose	linear	0.63
Non-Metformin/Insulin medication dose	linear	0.37
Insulin use	logistic	0.76
Bodyweight	linear	0.94

Information S8.7 Table 2: AIC and BIC values calculated from multilevel models with a fixed or random slope for each time-varying predictor (predictor as outcome with time as only exposure). Lower AIC/BIC values indicate a more parsimonious model fit and inform on whether predictors would be best described with fixed or randomly-varying trajectories.

Predictor	Fixed or Random time slope	AIC	BIC	Do random slopes improve model fit for predictor?
Dietary pattern score	Fixed	2762	2778	No
	Random	2766	2789	
Energy intake	Fixed	21747	21762	No
	Random	21742	21766	
Metformin dose	Fixed	23805	23821	Yes
	Random	23016	23039	
Non-Metformin/Insulin medication dose	Fixed	25223	25328	Yes
	Random	24143	24166	
Insulin use	Fixed	282	294	Yes
	Random	264	284	
Bodyweight	Fixed	16723	16738	Yes
	Random	15962	15985	

Information S8.8: Disaggregating variables into between- and within-person change over time

To separate the different sources of variation (cross-sectionally (between-persons) or longitudinally (within-persons)) inherent to variables measured repeatedly over time, glucose-lowering medications, energy intake and bodyweight were disaggregated into between- and within-person components through person-mean centring (41). Specifically, metformin dose was split into a time-invariant variable for the person-mean dose (i.e. average metformin dose across all timepoints) and a time-varying second variable for the deviation from a person's mean metformin dose at each given timepoint. These two disaggregated variables were added to models 1-3 as individual predictors. This process was repeated for non-metformin/insulin glucose-lowering medication dose, total energy intake and bodyweight. Dichotomous insulin use was disaggregated similarly by including in models 1-3 a person-mean insulin use over time variable (ranging from 0 to 1), but also including a dichotomous variable for insulin use at a given timepoint (instead of a variable denoting the deviation from the person-mean insulin use variable at each specific timepoint). The latter adjustment decision was to avoid any need to interpret model estimates that might represent a person's mean insulin use as <0, as this is not possible. However, as described in Information S8.7, glucose-lowering medications and bodyweight trajectories varied randomly but cannot be modelled as such due to limitations in Stata software. Effect estimates and their level of significance for these specific variables in models 1-3 will therefore not be interpreted directly but their inclusion allows adjustment for their potential confounding/mediating effects between dietary pattern score and HbA1c.

Table S8.21: Number of participants on diabetes medications in those with diet data at any timepoint, n (%).

	Timepoint				
	0m	**6m**	**1y**	**3y**	**6y**
Medication data available	379 (100%)	379 (100%)	379 (100%)	329 (86%)	305 (81%)
Metformin	129 (34%)	129 (34%)	148 (39%)	167 (51%)	191 (63%)
Sulphonylurea	32 (8%)	32 (8%)	34 (9%)	54 (16%)	66 (22%)
Glitazone	3 (1%)	3 (1%)	6 (2%)	10 (3%)	10 (3%)
Acarbose	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)
DPP4	0 (0%)	0 (0%)	0 (0%)	4 (1%)	21 (7%)
GLP1	0 (0%)	0 (0%)	0 (0%)	3 (1%)	13 (4%)
Insulin	0 (0%)	0 (0%)	2 (0.5%)	8 (2%)	15 (5%)

Table S8.22: Maximum doses for glucose-lowering medications other than insulin applied to analysis of Early-ACTID and DIRECT 2.2 (Chapter 6) data [450].

Drug type	**Drug**	**Max Dose (mg)**	**Weekly (W) or Daily (D)**
Alpha-glucosidase inhibitor	Acarbose	600	D
Biguanide	Metformin	3000	D
SGLT2	Dapagliflozin	10	D
SGLT2	Empagliflozin	25	D
DPP-4 inhibitor	Alogliptin	25	D
DPP-4 inhibitor	Linagliptin	5	D
DPP-4 inhibitor	Sitagliptin	100	D
GLP-1 agonist	Dulaglutide	1.5	W
GLP-1 agonist	Liraglutide	3	D
Sulphonylurea	Glibenclamide	15	D
Sulphonylurea	Gliclazide	320	D
Sulphonylurea	Glimepiride	6	D
Sulphonylurea	Glipizide	20	D
Sulphonylurea	Tolbutamide	2000	D

Table S8.23: Missing HbA1c (outcome) patterns in participants included within analyses sample (Models 1a-3).

HbA1c missingness indicator 1 assigned for sustained study attrition or to those who declined to take part in follow-up. Missingness pattern indicator 2 was assigned to all other missingness patterns not explained by missingness indicator 1.

HbA1c missingness pattern [a] (+ = available; . = missing)	**Number of missing values**	**Frequency**	**Missingness pattern indicator assigned**
+++++	0	293	-
+++..	2	47	1
++++.	1	32	1
+++.+	1	2	2
+.+..	3	2	2
++.++	1	1	2
+.+++	1	1	2
++...	3	1	1

[a] *Missing HbA1c patterns in order of time: 0-, 6-months, 1-, 3-, 6-years*

Table S8.24: Baseline characteristics of all ACTID participants and of analysis sample for assessing potential sample selection bias.

	All ACTID	**Sample**
N	593	352
Male	383 (65%)	231 (66%)
Age (years)	61 (53, 68)	62 (55, 68)
Disease duration (years)	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)
Weight (kg)	89.0 (80.0, 99.3)	86.9 (78.0, 96.5)
BMI (kg/m^2)	30.4 (27.8, 34.2)	29.5 (27.3, 33.1)
Total physical activity (cpm)	286 (218, 366)	287 (221, 367)
MVPA (mins/day)	21 (12, 36)	21 (11, 36)
IMD score	12.7 (7.2, 20.0)	12.5 (7.1, 19.1)
Smoker	48 (8%)	27 (8%)
HbA1c (mmol/mol)	48 (43, 54)	46 (42, 53)
HbA1c (%)	6.5 (6.1, 7.1)	6.4 (6.0, 7.0)
HOMA2-%B	83.6 (55.3, 123.2)	77.2 (52.6, 118.5)
HOMA2-IR	4.9 (3.4, 7.4)	4.6 (3.1, 7.0)
Metformin use	206 (35%)	118 (34%)
Metformin (%max dose)	0 (0, 33)	0 (0, 33)
Non-metformin/non-insulin medications use	56 (9%)	33 (9%)
Non-metformin/non-insulin medications (sum of %max doses)	0 (0, 0)	0 (0, 0)
Insulin use	0 (0%)	0 (0%)

Data presented as median (Q1, Q3) or n(%).

Table S8.25: Between- and within-person associations between differences in 'carb/fat balance' dietary pattern score and HbA1c change over time.

Between-person β's represent the change in HbA1c per 6 months associated with a 1-SD higher mean dietary pattern score over the course of the study (0-6 years). Within-person β's represent the change in HbA1c associated with a 1-SD increase in dietary pattern score above a person's mean dietary pattern score per 6 months.

		0-6m			6-12m		
Model	**n**	**β**	**95%CI**	**p**	**β**	**95%CI**	**p**
Between-person							
1	379	-2.73	-4.28, -1.18	**0.001**	-0.08	-2.02, 1.86	0.937
1a	352	-3.05	-4.71, -1.40	**<0.001**	0.21	-1.85, 2.27	0.840
2	352	-3.04	-4.70, -1.38	**<0.001**	0.32	-1.74, 2.38	0.761
3	352	-2.13	-3.76, -0.50	**0.010**	0.16	-1.84, 2.16	0.876
Within-person							
1	379	-0.94	-3.34, 1.46	0.441	1.58	-1.13, 4.28	0.254
1a	352	-1.29	-3.72, 1.15	0.300	1.74	-1.02, 4.48	0.217
2	352	-1.22	-3.66, 1.22	0.326	1.59	-1.16, 4.34	0.257
3	352	-0.89	-3.32, 1.53	0.472	1.43	-1.34, 4.21	0.312

1 – Random linear piecewise slope multilevel model for HbA1c (outcome) adjusted for continuous time, disaggregated between- and within-person dietary pattern scores and their interactions with time-period (exposures), disaggregated between- and within-person glucose-lowering medications (metformin dose, non-metformin/insulin dose and insulin use) and their interactions with time.

1a – Model 1 restricted to sample with complete sets of covariate data for ≥1 timepoint.

2 – Model 1a adjusted for baseline sex, age, smoking status, total physical activity and energy under-reporting status (potential confounders) and their interactions with time.

3 – Model 2 adjusted for disaggregated between- and within-person energy intakes and weight (potential mediators) and their interactions with time.

Table S8.26: Explained nutrient variation and correlations for 'carb/fat balance' dietary patterns derived independently at 0-, 6-months, 1-, 3- and 6-years.

Dietary pattern score/nutrient correlation coefficients for each nutrient at 1-, 3- and 6-years can be considered inverted relative to 0m and 6m correlations as an artefact of the reduced-rank regression procedure's final iteration. Multiplying all food group pattern loadings at 1-, 3- and 6-years by -1 moves the direction of association of the dietary pattern score with its nutrient response variables to be in line with those seen at 0- and 6-months. Projecting this single, 0-month dietary pattern structure onto other timepoint data allows for a meaningful analysis of changes in a single dietary pattern score over time.

	Explained variation (%)							Correlation coefficient				
Timepoint	**Nutrient intake (total)**	**Starches and sugars (%)**	**Fibre density (g/MJ)**	**SFA (%)**	**MUFA (%)**	**PUFA (%)**	**Food intake (total)**	**Starches and sugars (%)**	**Fibre density (g/MJ)**	**SFA (%)**	**MUFA (%)**	**PUFA (%)**
0m	36.2	53.9	45.1	40.9	39.9	1.4	2.1	0.74	0.68	-0.64	-0.63	-0.12
6m	39.2	57.5	47.4	45.7	44.2	1.1	2.4	0.76	0.69	-0.68	-0.67	-0.10
1y	40.0	57.0	45.2	44.5	51.1	2.3	2.7	-0.75	-0.67	0.67	0.71	0.15
3y	45.8	67.0	38.3	53.6	59.4	10.6	2.6	-0.81	-0.62	0.73	0.77	0.33
6y	38.4	56.9	43.9	44.8	43.7	2.9	2.3	-0.75	-0.66	0.67	0.66	0.17

SFA - saturated fat; MUFA - mono-unsaturated fat; PUFA - poly-unsaturated fat.

Table S8.27: Tucker's congruence coefficients [342] between dietary patterns derived at baseline (0m) and dietary patterns derived at all other timepoints for demonstrating pattern structural similarity between timepoints.

Congruence was classed as 'fair' between 0m and all other timepoints except at 3-years. Scoring intakes at each timepoint relative to the 0m dietary pattern thus captures sufficient variation in diet at each timepoint but less so at 3 years. Negative congruence coefficients can be interpreted as essentially being 'inverted' 0m pattern scores, as an artefact of the reduced-rank regression's final iteration (see Table S8.3 and Table S8.26).

Pattern comparison	Congruence coefficient	Congruence
0m - 6m	0.89	fair
0m – 1y	-0.87	fair
0m - 3y	-0.78	poor
0m - 6y	-0.85	fair

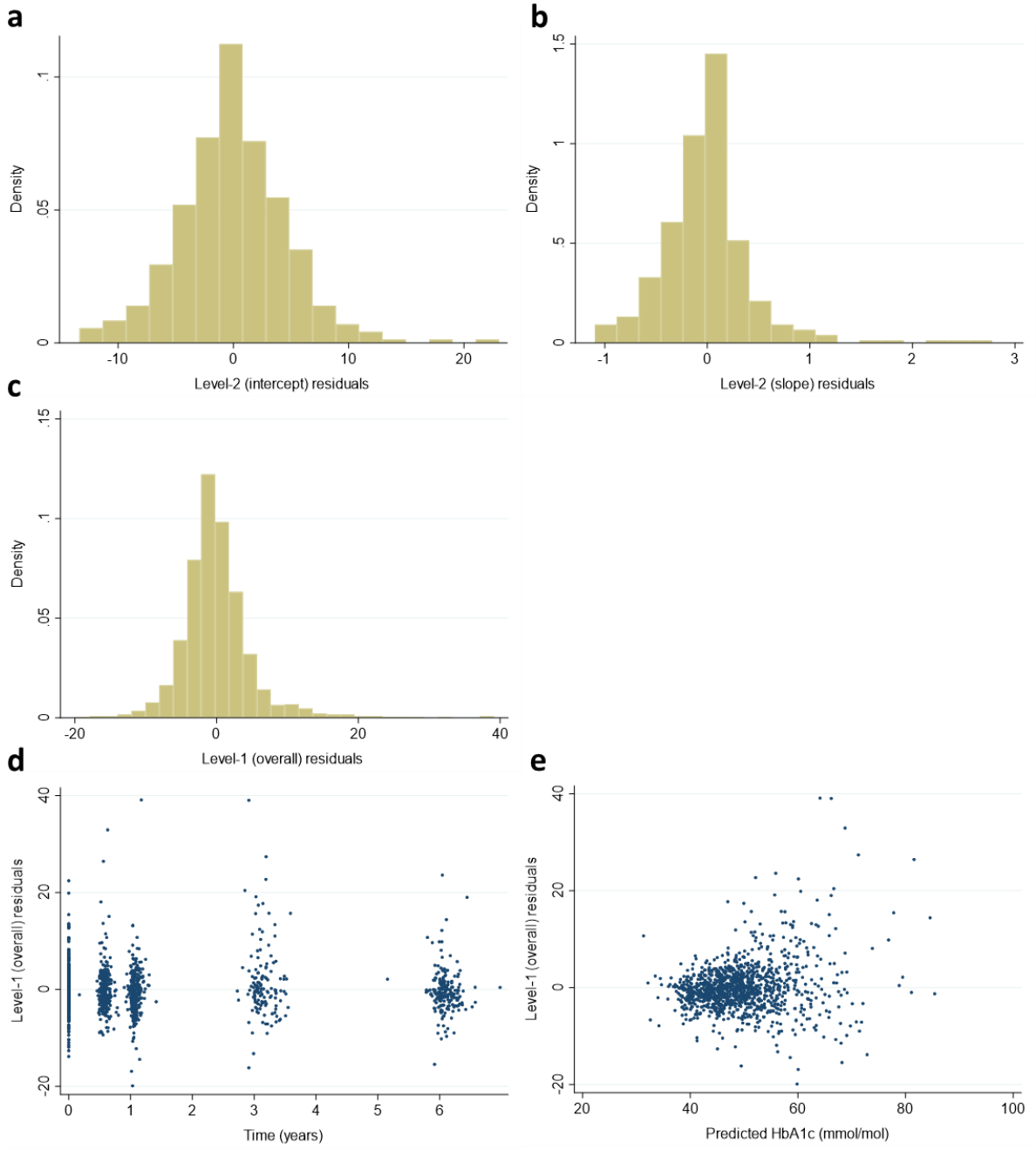
Table S8.28: Associations between HbA1c missingness pattern indicators and exposure (dietary pattern scores) and outcome (HbA1c) obtained via simple logistic regression.

HbA1c missingness patterns were not associated with main analysis model exposure or outcome and thus would not appear to be confounding associations between model exposure and outcome. β's and their 95%CI are presented as Odds Ratios.

		Missingness pattern indicator 1			**Missingness pattern indicator 2**		
N	**Exposure Variable**	**β**	**95%CI**	**p**	**β**	**95%CI**	**p**
324	Carb/fat balance dietary pattern score 0m	0.93	0.66, 1.30	0.667	0.84	0.39, 1.84	0.671
286	Carb/fat balance dietary pattern score 6m	0.85	0.57, 1.26	0.420	1.35	0.55, 3.31	0.518
303	Carb/fat balance dietary pattern score 1y	1.07	0.77, 1.49	0.666	1.22	0.56, 2.66	0.608
137	Carb/fat balance dietary pattern score 3y	-	-	-	0.78	0.14, 4.21	0.772
197	Carb/fat balance dietary pattern score 6y	3.36	0.21, 2.90	0.389	0.86	0.25, 2.97	0.806
379	HbA1c 0m	0.99	0.97, 1.02	0.667	1.02	0.97, 1.07	0.414
376	HbA1c 6m	1.00	0.98, 1.02	0.914	0.99	0.92, 1.06	0.714
377	HbA1c 1y	1.01	0.99, 1.04	0.255	1.00	0.93, 1.07	0.954
327	HbA1c 3y	0.99	0.95, 1.02	0.468	0.99	0.93, 1.05	0.769
297	HbA1c 6y	-	-	-	1.00	0.96, 1.05	0.893

Figure S8.13: Model 3 residual diagnostics.

a - Histogram of model intercept residuals to assess assumptions of level-2 intercept residual normality; b - Histogram of model slope residuals to assess assumptions of level-2 slope residual normality; c – Histogram of overall model residuals to assess assumptions of level-1 residual normality; d - Overall model residuals plotted against time to assess assumptions of homoscedasticity of model residuals over time; e - Overall model residuals plotted against model-predicted HbA1c values to assess assumptions of residual independence from predicted values.



8.4 Supplementary Materials for Chapter 6 (Study 4)

Table S8.29: Explained nutrient variation and correlations for the first dietary patternss derived independently at 0-, 18-, and 36-months in DIRECT cohort 2.2 (n=688, n=491 and n=404 respectively).

The first dietary patterns explained the most nutrient intermediate variation and were thus retained for further analysis.

			Explained variation (%)							Correlation coefficient				
Timepoint	**Dietary pattern**	**N**	**Responses (total)**	**Starches and Sugars (%)**	**Fibre density (g/MJ)**	**SFA (%)**	**MUFA (%)**	**PUFA (%)**	**Food intake (total)**	**Starches and Sugars (%)**	**Fibre density (g/MJ)**	**SFA (%)**	**MUFA (%)**	**PUFA (%)**
0m	**1**	688	31.8	55.0	17.7	35.2	43.2	7.8	1.6	-0.74	-0.42	0.59	0.66	0.28
18m	**1**	491	36.5	61.5	22.6	34.2	46.3	17.7	1.9	-0.78	-0.48	0.59	0.68	0.42
36m	**1**	404	35.3	61.9	22.6	33.8	46.7	11.7	1.7	-0.79	-0.48	0.58	0.68	0.34

SFA - saturated fat; MUFA - mono-unsaturated fat; PUFA - poly-unsaturated fat

Table S8.30: Tucker's congruence coefficients [342] between dietary patterns derived at baseline (0m), 18-months (18m) and 36-months (36m) for exploring pattern structural similarity across timepoints.

Congruence was classed as 'poor' between all timepoints (CC<0.85), suggesting group-level dietary patterns were not structurally similar across time. Scoring intakes at each timepoint relative to the baseline dietary pattern structure, for example, appeared unsuitable for capturing sufficient variation in diet intakes at each individual timepoint.

Pattern comparison	Congruence coefficient	Congruence
0m - 18m	0.81	poor
0m – 36m	0.80	poor
18m – 36m	0.78	poor

Table S8.31: Tucker's congruence coefficients [342] between dietary patterns derived at baseline (0m), 18-months (18m) and 36-months (36m) for exploring pattern structural similarity across timepoints in those with dietary data at all timepoints (n=333).

Congruence was again classed as poor between all timepoints, suggesting group-level dietary patterns were not structurally similar across time, even when assessed in the same individuals across time.

Pattern comparison	Congruence coefficient	Congruence
0m - 18m	0.78	poor
0m – 36m	0.71	poor
18m – 36m	0.80	poor

Table S8.32: Tucker's congruence coefficients [342] between dietary patterns derived in participants of the Early-ACTID trial from a single day's diet at each timepoint (instead of from four-days of diet at each timepoint, as was measured) for exploring pattern structural similarity across timepoints when using a shorter-term diet measure.

Dietary pattern structural similarity is now poor for comparisons between baseline and other timepoints, instead of 'fair' when dietary pattern were derived from the full four days of diet data (data taken from Table S8.27).

	All data from four-day diet diary		**24-hrs data from four-day diet diary**	
Pattern timepoint comparison	**Congruence coefficient**	**Congruence**	**Congruence coefficient**	**Congruence**
0m - 6m	0.89	fair	0.81	poor
0m – 1y	-0.87	fair	0.78	poor
0m - 3y	-0.78	poor	0.63	poor
0m - 6y	-0.85	fair	0.81	poor

Information S8.9: Longitudinal and Random effects modelling.

Repeating methods used in Study 3 (Information S8.7), to assess whether changes over time in model predictors were significant enough to require modelling longitudinally (rather than only adjusting for baseline values), intraclass correlation coefficients (ICC) were calculated from linear or logistic empty-means, random intercept models, with no exposure and with metformin dose, non-metformin/insulin dose, insulin use and bodyweight as separate outcomes. Although ICC values for insulin use and bodyweight were found to be close to unity (ICC=0.97), all predictors shown in Information S8.9 Table 1 were modelled as time-varying in order to replicate methods used in Chapter 5 as closely as possible.

Dietary pattern scores (main models 1-3 exposure) were calculated for each participant from average dietary intakes over 0-36 months and were thus modelled as time-invariant, requiring fixed trajectory modelling only. Other predictors in main models 1-3 which were time-varying (medications and bodyweight) were assessed for whether their longitudinal change would be best described with fixed or random trajectories, as described in Information S8.7. As also stated in Information S8.7, limitations in Stata software to model both randomly-varying predictors and randomly-varying outcomes, restricts modelling of predictor trajectories in models 1-3 to having fixed slopes only. Assessment of AIC/BIC values from models with fixed or random slopes for each time-varying predictor will therefore help determine whether estimates of these specific predictors in main models 1-3 are potentially biased or not by the modelling method used. AIC/BIC values in Information S8.9 Table 2 indicates that modelling random trajectories for glucose-lowering medications and bodyweight should not be interpreted directly due to their trajectories varying randomly over time. They will therefore suffer from incomplete disaggregation into their between- and within-person effects when using the person-mean centring disaggregation method (Information S8.7). However, glucose-lowering medications and bodyweight are not the main exposures of interest in this study. They remain suitable to account for potential confounding/mediation of dietary pattern and HbA1c associations in models 1-3, regardless of whether their specific estimates can be interpreted directly.

Information S8.9 Table 1: Intra-class correlation coefficients (ICC) for main analysis models 1-3 predictors that are measured repeatedly over time. The ICC are calculated from linear/logistic empty means, random intercept models with each predictor as independent outcomes. The ICC value (range 0-1) represents the proportion of variation over time between-persons versus within-persons.

Predictor	Model type (multilevel)	ICC
Metformin dose	linear	0.80
Non-Metformin/Insulin medication dose	linear	0.37
Insulin use	logistic	0.97
Bodyweight	linear	0.97

Information S8.9 Table 2: AIC and BIC values calculated from models with fixed or random slopes for each time-varying predictor from models 1-3. Lower AIC/BIC values indicate a more parsimonious model fit and reveal whether predictors are best described with fixed or randomly-varying trajectories. Insulin use results are not shown as neither fixed nor random effects logistic models converged.

Predictor	Fixed or Random time slope	AIC	BIC	Do random slopes improve model fit for predictor?
Metformin dose	Fixed	950	968	Yes
	Random	405	433	
Non-Metformin/Insulin medication dose	Fixed	-1255	-1237	Yes
	Random	-2915	-2888	
Bodyweight	Fixed	16144	16162	Yes
	Random	15940	15967	

Table S8.33: Number of participants in models 1a-3 (n=686) on glucose-lowering medications at each timepoint (n(%)).

Metformin was the most commonly prescribed medication.

	Timepoint (months)				
Medication	**0**	**9**	**18**	**27**	**36**
Metformin	235 (34%)	256 (37%)	286 (42%)	302 (44%)	316 (46%)
Sulphonylurea	0 (0%)	3 (0.4%)	10 (1%)	16 (2%)	28 (4%)
DPP4	0 (0%)	2 (0.3%)	3 (0.4%)	5 (1%)	10 (1%)
GLP1	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	4 (0.6%)
SGLT-2	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	4 (0.6%)
Insulin	0 (0%)	2 (0.3%)	4 (0.6%)	4 (0.6%)	6 (1%)

Table S8.34**:** Variation in measurement times for each measurement wave.

To avoid information loss, time was modelled as a continuous variable within Models 1-3 rather than protocol-rounded values.

Protocol measurement time (months)	**Actual measurement time (months)**			
	Mean (SD)	**Median (Q1, Q3)**	**Min**	**Max**
0	0.0 (0.0)	0.0 (0.0, 0.0)	0.0	0.0
9	9.1 (0.4)	9.0 (8.9, 9.2)	7.6	12.7
18	18.2 (0.8)	18.1 (17.9, 18.4)	14.2	24.3
27	27.0 (1.7)	26.9 (26.6, 27.2)	26.0	29.4
36	36.3 (1.2)	36.1 (35.9, 36.5)	29.1	46.0

Table S8.35: Baseline descriptive dietary and sample characteristics in extreme quintiles of mean 'carb/fat balance' dietary pattern score.

Highest loading food group intakes in median (quartile 1, quartile 3) g/day are presented to indicate average amounts of foods consumed. Percentage of consumers of these food groups indicate the number of individuals consuming any amount of these foods at any timepoint. Median 'Meat substitutes' intake is zero, as observed in data from Early-ACTID, but should be interpreted in context of percentages of consumers being very low (2% of sample).

		Whole sample	**Quintile 1**	**Quintile 5**
N		683	138	137
Carb/fat balance dietary pattern score		-0.24 (-0.97, 0.50)	-1.76 (-2.33, -1.47)	1.09 (0.82, 1.42)
Energy intake (kJ)		7340 (6006, 8861)	8727 (7530, 10007)	6690 (5464, 8327)
Total carbohydrate (%TEI)		45.4 (40.6, 51.4)	39.1 (33.5, 42.5)	54.2 (50.3, 58.8)
Starches and sugars (%TEI)		43.8 (39.0, 49.5)	37.8 (32.2, 41.4)	52.2 (48.7, 56.9)
Fibre (g/MJ)		1.9 (1.5, 2.3)	1.5 (1.2, 1.7)	2.4 (2.0, 2.9)
Protein (%TEI)		18.9 (16.1, 21.8)	19.1 (16.2, 22.9)	17.2 (15.6, 21.4)
Total fat (%TEI)		34.3 (29.3, 39.0)	41.0 (37.1, 44.9)	27.6 (23.5, 31.5)
SFA (%TEI)		12.2 (10.0, 14.8)	14.9 (12.2, 17.5)	9.4 (7.3, 11.5)
MUFA (%TEI)		11.5 (9.4, 13.5)	14.0 (11.7, 15.9)	8.5 (6.8, 10.5)
PUFA (%TEI)		5.3 (4.0, 6.7)	6.0 (4.9, 7.5)	4.7 (3.2, 5.9)
Alcohol (%TEI)		0 (0, 2.5)	0 (0, 3.8)	0 (0, 0)
Highest positive loading food groups				
Fruit (fresh), g/d		114 (45, 90)	100 (33, 162)	187 (100, 304)
	% consumers	*89*	*78*	*89*
Low fat milk, g/d		153 (41, 268)	110 (0, 233)	204 (110, 315)
	% consumers	*88*	*70*	*89*
Boiled/baked potatoes, g/d		20 (0, 87)	0 (0, 60)	0 (0, 100)
	% consumers	*56*	*41*	*45*
Legumes, g/d		0 (0, 10)	0 (0, 0)	0 (0, 40)
	% consumers	*31*	*18*	*39*
Meat substitutes, g/d		0 (0, 0)	0 (0, 0)	0 (0, 0)
	% consumers	*2*	*1*	*4*
Highest negative loading food groups				
Higher fat processed meats, g/d		3 (0, 34)	14 (0, 50)	0 (0, 5)
	% consumers	*55*	*62*	*26*
Butter and animal fats, g/d		0 (0, 6)	2 (0, 13)	0 (0, 0)
	% consumers	*43*	*52*	*20*

Red meat, g/d	0 (0, 33)	0 (0, 57)	0 (0, 0)
% consumers	*36*	*43*	*16*
Low fibre bread, g/d	25 (0, 60)	37 (0, 66)	0 (0, 45)
% consumers	*70*	*72*	*47*
Fried/roast, chips & other potato with added fat, g/d	0 (0, 47)	0 (0, 57)	0 (0, 45)
% consumers	*42*	*40*	*34*
Energy under-reporters (n(%))	353 (52%)	46 (33%)	77 (56%)
Male (n(%))	406 (59%)	88 (64%)	71 (52%)
Age (years)	63 (57, 68)	63 (56, 67)	62 (57, 69)
Disease duration (years)	1.0 (0.5, 1.6)	1.2 (0.6, 1.6)	0.8 (0.5, 1.4)
Smoker (n(%))	97 (14%)	19 (14%)	21 (15%)
Mean physical activity intensity (hpfVM; mg)	34 (28, 40)	36 (29, 41)	34 (28, 41)
MVPA (mins/day)	41 (30, 53)	45 (34, 56)	44 (30, 54)
Weight (kg)	88.2 (76.8, 100.8)	86.1 (78.3, 102.4)	88.0 (75.7, 100.8)
BMI (kg/m^2)	29.8 (26.7, 33.7)	29.7 (26.3, 33.5)	29.6 (27.6, 33.8)
HbA1c (mmol/mol)	46 (43, 50)	47 (42, 51)	46 (42, 49)
HbA1c (%)	6.4 (6.1, 6.7)	6.5 (6.0, 6.8)	6.4 (6.0, 6.6)
HOMA2-%B	91.2 (70.0, 114.3)	88.9 (68.2, 105.8)	96.0 (76.5, 120.6)
HOMA2-IR	2.5 (1.9, 3.2)	2.5 (1.9, 3.3)	2.4 (2.0, 3.1)
Metformin use (n(%))	232 (34%)	48 (35%)	34 (25%)
Metformin (%max dose)	0 (0, 17)	0 (0, 33)	0 (0, 0)
Non-metformin/insulin medication use (n(%))	0 (0%)	0 (0%)	0 (0%)
Non-metformin/insulin medications (sum of %max doses)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Insulin use (n(%))	0 (0%)	0 (0%)	0 (0%)

All data presented as n (%) or median (quartile 1, quartile 3). *TEI – total energy intake; SFA - saturated fat; MUFA - monounsaturated fat; PUFA - polyunsaturated fat; hpfVM – high-pass filter vector magnitude; MVPA – moderate-to-vigorous activity; BMI – body mass index; HOMA2-%B – homeostasis model assessment of beta-cell function; HOMA2-IR – homeostasis model assessment of insulin resistance.*

Table S8.36: Baseline characteristics of all eligible DIRECT 2.2 participants versus analysis sample for assessing potential selection bias.

Values presented as median (quartile 1, quartile 3) or n(%).

	All DIRECT	**Sample**
N	771	686
Research centre		
Exeter, England	135 (18%)	107 (16%)
Newcastle, England	164 (21%)	159 (23%)
Dundee, Scotland	164 (21%)	160 (23%)
Amsterdam, Netherlands	162 (21%)	137 (20%)
Copenhagen, Denmark	51 (7%)	38 (6%)
Lund, Sweden	95 (12%)	85 (12%)
Male (n(%))	443 (57%)	408 (59%)
Age (years)	63 (57, 68)	63 (57, 68)
Disease duration (years)	1.0 (0.6, 1.6)	1.0 (0.5, 1.6)
Weight (kg)	88.2 (77.3, 100.8))	88.2 (76.8, 100.8)
BMI (kg/m^2)	29.8 (26.7, 33.9)	29.7 (26.7, 33.7)
Mean physical activity intensity (hpfVM; mg)	34 (28, 40)	34 (28, 40)
MVPA (mins/day)	41 (30, 53)	41 (30, 53)
Smoker (n(%))	106 (14%)	97 (14%)
HbA1c (mmol/mol)	46 (43, 50)	46 (43, 50)
HbA1c (%)	6.4 (6.1, 6.7)	6.4 (6.1, 6.7)
HOMA2-%B	90.5 (70.0, 114.2)	91.0 (70.0, 114.2)
HOMA2-IR	2.5 (1.9, 3.2)	2.5 (1.9, 3.2)
Metformin use (n(%))	266 (35%)	235 (34%)
Metformin (%max dose)	0 (0, 17)	0 (0, 17)
Non-metformin/insulin medication use (n(%))	0 (0%)	0 (0%)
Non-metformin/insulin medications (sum of %max doses)	0 (0, 0)	0 (0, 0)
Insulin use (n(%))	0 (0%)	0 (0%)

BMI – body mass index; hpfVM – high-pass filter vector magnitude; MVPA – moderate-to-vigorous activity; HOMA2-%B – homeostasis model assessment of beta-cell function; HOMA2-IR – homeostasis model assessment of insulin resistance.

Table S8.37: Missing HbA1c (outcome) patterns in participants included within analysis models 1-3 (n=686).

HbA1c missingness indicator 1 was assigned for study attrition passed a given timepoint. HbA1c missingness pattern indicator 2 was assigned to all other missingness patterns not explained by missingness indicator 1. As HbA1c was measured in only n=27 participants at 27-months, missing 27-month values were considered missing completely at random (MCAR) and were not used to inform assignment of missingness pattern indicators.

HbA1c missingness pattern [a] (+ = available; . = missing)	**Number of missing values**	**Frequency**	**Missingness pattern indicator assigned**
+++++	0	26	-
+++.+	0	504	-
++++.	1	6	1
+++..	2	69	1
+.+..	3	4	1
++…	3	25	1
+….	4	23	1
++..+	2	7	2
.++++	1	3	2
+…+	3	1	2
+.+++	1	1	2
+.+.+	2	17	2

[a] *Missing HbA1c patterns in order of time: 0-, 9-, 18-, 27-, and 36-months*

Table S8.38: Associations between HbA1c missingness pattern indicators and exposure (mean dietary pattern score) and outcome (HbA1c at each timepoint) obtained via simple logistic regression.

HbA1c missingness patterns did not associate with main analysis model exposure or outcome. Main analysis models thus needed no further adjustment for predictor/proxy variables of missingness as associations between model exposure and outcome do not appear to be confounded by missing data. β's and their 95%CI are presented as odds ratios.

		Missingness pattern indicator 1			Missingness pattern indicator 2		
N	**Exposure Variable**	**β**	**95%CI**	**p**	**β**	**95%CI**	**p**
686	Mean carb/fat balance dietary pattern score	1.06	0.90, 1.24	0.514	0.80	0.62, 1.03	0.085
683	HbA1c 0m	1.00	0.97, 1.04	0.881	0.99	0.93, 1.06	0.758
640	HbA1c 9m	1.02	0.99, 1.05	0.167	0.99	0.91, 1.08	0.890
630	HbA1c 18m	1.00	0.97, 1.02	0.777	1.02	0.98, 1.06	0.238
36	HbA1c 27m	0.92	0.79, 1.06	0.252	1.07	0.91, 1.24	0.417
559	HbA1c 36m	-	-	-	1.01	0.98, 1.05	0.546

Table S8.39: Average dietary intakes calculated from different numbers of total 24-hr diet records; 1-3 days (as used for analysis within models 1-3; N=686), 1 random day (N=686), 2 random days (N=433), or 3 complete days (N=307).

Average dietary intakes do not appear to differ substantially by the number of 24-hr records used to calculate these averages. Dietary intakes of participants included in Models 1-3 do not appear to be strongly biased, therefore, by the number of diet measures returned.

	Number of 24-hr records averaged over time			
Dietary component	**1-3 days**	**3 complete days**	**2 random days**	**1 random day**
N	686	307	433	686
Carb/fat balance dietary pattern score	-0.24 (-0.97, 0.50)	-0.39 (-0.99, 0.19)	-0.46 (-1.08, 0.27)	-0.16 (-1.06, 0.69)
Energy intake (kJ)	7365 (6009, 8861)	7598 (6325, 9028)	7530 (6130, 8882)	7166 (5834, 8927)
Total carbohydrate (%E)	45.4 (40.6, 51.3)	44.1 (40.4, 49.1)	44.6 (39.5, 50.1)	46.1 (39.5, 52.9)
Starches and sugars (%E)	43.8 (39.0, 49.5)	42.6 (39.0, 47.2)	43.1 (38.3, 48.3)	44.4 (38.0, 51.0)
Fibre (g/MJ)	1.9 (1.5, 2.3)	1.9 (1.5, 2.3)	1.9 (1.5, 2.3)	1.9 (1.4, 2.5)
Protein (%E)	18.9 (16.2, 21.8)	19.3 (16.7, 21.9)	19.0 (16.6, 21.9)	18.6 (15.4, 22.1)
Total fat (%E)	34.3 (29.3, 39.0)	35.4 (31.1, 39.3)	35.3 (30.5, 39.6)	34.5 (28.4, 40.4)
SFA (%E)	12.2 (10.0, 14.8)	12.8 (10.9, 15.1)	12.8 (10.8, 15.2)	12.2 (9.3, 15.2)
MUFA (%E)	11.5 (9.4, 13.5)	11.7 (10.0, 13.5)	11.7 (9.7, 14.0	11.3 (8.8, 14.3)
PUFA (%E)	5.3 (4.0, 6.7)	5.3 (4.3, 6.7)	5.3 (4.1, 6.7)	5.2 (3.5, 7.1)
Alcohol (%E)	0 (0, 2.5)	0 (0, 3.5)	0 (0, 2.8)	0 (0, 0)

Table S8.40: Associations between differences in mean 'carb/fat balance' dietary pattern score and rate of change in HbA1c in those with complete diet data at 0-, 18- and 36-months of the DIRECT 2.2 study.

β's represent the change in HbA1c per year associated with a 1-SD higher mean dietary pattern score over the course of the study.

Model	n	β	95%CI	p
1	326	-0.15	-0.46, 0.16	0.339
1a	307	-0.11	-0.42, 0.19	0.458
2	307	-0.10	-0.41, 0.21	0.545
3	307	-0.12	-0.42, 0.19	0.456

1 – Random linear slope multilevel model for HbA1c (outcome) adjusted for continuous time, dietary pattern score and its interaction with time, disaggregated between- and within-person glucose-lowering medication (namely metformin, non-metformin/insulin and insulin) doses and their interactions with time.

1a – Model 1 restricted to sample with complete sets of covariate data for at least one timepoint.

2 – Model 1a adjusted for baseline sex, age, smoking status, mean physical activity intensity and energy under-reporting status (potential confounders) and their interactions with time.

3 – Model 2 adjusted for mean energy intake and disaggregated between- and within-person bodyweight (potential mediators) and their interactions with time.

Table S8.41: Associations between differences in mean 'carb/fat balance' dietary pattern score and rate of change in HbA1c in the DIRECT 2.2 study, modelling HbA1c as nested within participants (level 2 in a multilevel model) who are nested within research centres (level 3).

β's represent the change in HbA1c per year associated with a 1-SD higher mean dietary pattern score over the course of the study.

Model	n	β	95%CI	p
1	748	-0.05	-0.25, 0.14	0.573
1a	686	0.01	-0.19, 0.20	0.956
2	686	0.02	-0.18, 0.22	0.840
3	686	-0.03	-0.22, 0.17	0.770

1 – Random linear slope multilevel model for HbA1c (outcome) adjusted for continuous time, dietary pattern score and its interaction with time, disaggregated between- and within-person glucose-lowering medication (namely metformin, non-metformin/insulin and insulin) doses and their interactions with time. HbA1c is modelled as nested within participants (level-2) who are nested within research centres (level 3).

1a – Model 1 restricted to sample with complete sets of covariate data for at least one timepoint.

2 – Model 1a adjusted for baseline sex, age, smoking status, mean physical activity intensity and energy under-reporting status (potential confounders) and their interactions with time.

3 – Model 2 adjusted for mean energy intake and disaggregated between- and within-person bodyweight (potential mediators) and their interactions with time.

Table S8.42: Comparison of characteristics at baseline for participants analysed using models 1a-3 in Early-ACTID (study 3) and DIRECT 2.2 (study 4).

	Early-ACTID	**DIRECT 2.2**
N (models 1a-3)	352	686
Male	231 (66%)	408 (59%)
Age (years)	62 (55, 68)	63 (57, 68)
Duration of disease (years)	0.5 (0.4, 0.6)	1.0 (0.5, 1.6)
Weight (kg)	86.9 (78.0, 96.5)	88.2 (76.8, 100.8)
BMI (kg/m^2)	29.5 (27.3, 33.1)	29.7 (26.7, 33.7)
MVPA (mins/day)	21 (11, 36)	41 (30, 53)
Smoker	27 (8%)	97 (14%)
HbA1c (mmol/mol)	46 (42, 53)	46 (43, 50)
HbA1c (%)	6.4 (6.0, 7.0)	6.4 (6.1, 6.7)
HOMA2-%B	77 (53, 119)	91 (70, 114)
HOMA2-IR	4.6 (3.1, 7.0)	2.5 (1.9, 3.2)
Metformin use	118 (34%)	235 (34%)
Metformin (%max dose)	0 (0, 33)	0 (0, 17)
Non-metformin/insulin medication use	33 (9%)	0 (0%)
Non-metformin/insulin medications (sum of %max doses)	0 (0, 0)	0 (0, 0)
Insulin use	0 (0%)	0 (0%)

Data presented as median (quartile 1, quartile 3) or n(%).

Table S8.43: Comparison of baseline dietary characteristics for participants analysed using models 1a-3 in Early-ACTID (study 3) and DIRECT 2.2 (study 4).

		Early-ACTID	DIRECT 2.2
n at baseline (models 1a-3)		302	683
Under-reporters		127 (42%)	354 (52%)
Carb/fat balance dietary pattern score (SD)		0.04 (-0.53, 0.49)	-0.24 (-0.97, 0.50)
Energy intake (kJ)		7347 (6146, 8591)	7365 (6009, 8861)
Total carbohydrate (%TEI)		45.4 (40.6, 49.8)	45.4 (40.6, 51.3)
Starches and sugars (%TEI)		43.5 (39.1, 47.8)	43.8 (39.0, 49.5)
Fibre (g/MJ)		2.2 (1.8, 2.6)	1.9 (1.5, 2.3)
Protein (%TEI)		17.9 (16.0, 20.0)	18.9 (16.2, 21.8)
Total fat (%TEI)		33.8 (30.2, 37.4)	34.3 (29.3, 39.0)
SFA (%TEI)		11.0 (9.4, 13.2)	12.2 (10.0, 14.8)
MUFA (%TEI)		12.1 (10.5, 13.7)	11.5 (9.4, 13.5)
PUFA (%TEI)		6.5 (5.3, 7.9)	5.3 (4.0, 6.7)
Alcohol (%TEI)		2.9 (0.0, 7.8)	0.0 (0.0, 2.5)
Highest positive loading food groups			
Fruit (fresh), g/d		157 (90, 236)	114 (45, 190)
	% consumers	93	81
Low fat milk, g/d		180 (110, 250)	153 (41, 268)
	% consumers	92	81
Boiled/baked potatoes, g/d		44 (0, 78)	20 (0, 87)
	% consumers	71	51
Legumes, g/d		18 (0, 45)	0 (0, 10)
	% consumers	69	28
Meat substitutes, g/d		0 (0, 0)	0 (0, 0)
	% consumers	2	2
Highest negative loading food groups			
Higher fat processed meats, g/d		10 (0, 30)	3 (0, 34)
	% consumers	57	51
Butter & animal fats, g/d		0 (0, 0)	0 (0, 6)
	% consumers	23	38
Red meat, g/d		17 (0, 34)	0 (0, 33)
	% consumers	55	34
Low fibre bread, g/d		0 (0, 38)	25 (0, 60)
	% consumers	49	63
Fried/roast, chips & other potato with added fat, g/d		38 (0, 69)	0 (0, 47)
	% consumers	69	39

Data presented as median (quartile 1, quartile 3) or n(%).

Figure S8.14: Model 3 residual diagnostics.

a - Histogram of model intercept residuals to assess assumptions of level-2 intercept residual normality; b - Histogram of model slope residuals to assess assumptions of level-2 slope residual normality; c – Histogram of overall model residuals to assess assumptions of level-1 residual normality; d- Overall model residuals plotted against time to assess assumptions of homoscedasticity of model residuals over time; e - Overall model residuals plotted against model-predicted HbA1c values to assess assumptions of residual independence from predicted values.