BOOK 1

A systematic review of the glycaemic response to foods and health

Geoffrey Livesey B.Sc., Ph.D., R.P.H.Nutr[1].

Richard Taylor B.Sc, MSc.[1]

Toine Hulsof B.Sc. Ph.D. [2]

1. Independent Nutrition Logic Ltd,

Pealerswell House, 21 Bellrope Lane,

Wymondham, Norfolk NR18 0QX United Kingdom

Tel: +44-1953-606689; Fax: +44-1953-600218

Email: glivesey@inlogic.co.uk

2. Kellogg Europe, Den Bosch, The Netherlands

Keywords: Food, health, blood glucose, diabetes, coronary heart disease, meta-analysis, glycaemic response, glycaemic index, glycaemic load, total carbohydrate, available carbohydrate, unavailable carbohydrate.

Acknowledgement

herein are those of the author(s) and do not necessarily represent the view of ILSI Europe.

Foreword by the first author

Since the Workshop in Nice 6-8th Dec 2006, aspects of the report have been published elsewhere:

Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health a systematic review and meta-analysis: relations between dietary glycemic properties and health outcomes. Am J Clin Nutr 2008;87:258S-68S.

Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health a systematic review and meta-analysis: the database, study characteristics, and macronutrient intakes. Am J Clin Nutr 2008;87:223S-36S

Minor modifications to the report have also been made to correct typographical errors (transposed numerals, incorrect decimal places, missing negative signs etc, together with general but not exhaustive minor editing. A missing table and a figure omitted during last minute preparation of the draft for the workshop have been reinstated. A number of stylistic changes were made to make the text easier on the eye (in particular referencing to material in the annexes). Some duplicate matter has been removed, and some sentence constructions have been reworked to help them make sense or remove ambiguity. Outputs from statistical analyses have been checked against re-run computer outputs to eliminate transfer errors. The list of abbreviations has been extended to include more of those used and defined in text and tables previously. Some workshop participants requested more information about individual studies, designs, duration of treatment, dose, number of participants etc to be tabulated so as to obtain an overview of the studies. This request has been accommodated by providing an extensive table in the first of the above two references.

Geoff Livesey

Foreword
ILSI Europe Dietary Carbohydrates Task Force

The ILSI Europe Dietary Carbohydrates Task Force commissioned a series of meta-analyses of intervention studies on glycaemic response and health. The resulting report comprised two volumes (books) that describe the work undertaken and present the preliminary results and conclusions. These are described primarily in Book 1 with additional supporting data presented in the tables and figures of Book 2. These served as the working documents for an ILSI Europe Workshop held in Nice in December 2006. After the workshop the meta-analyses and key conclusions were summarised in two papers that, together with papers from other speakers at the workshop, have been published as Supplement (1) to the January 2008 issue of the American Journal of Clinical Nutrition (AJCN, Volume 87). The Supplement focuses on the general approach, outcomes, and conclusions of the meta-analyses, and is available from the Journal's website.

Hard copy of the Supplement can also be obtained without charge from ILSI Europe at publications@ilsieurope.be.

Note that comments, typos, and suggestions for presentation arising during the workshop are not addressed within these books, though are taken into account in the subsequent publications in AJCN. Ideas and findings made first in this work and reported in the books should be credited to ILSI Europe and its authors. Where material is present in both the Books and in the AJCN publication, the peer reviewed AJCN should be cited in any further works. Whereas the papers in AJCN underwent peer review, the additional information in the two workshop books did not. Material in the books but not in the AJCN publications should, therefore, not be used or cited without due caution. Wherever the outcomes of the meta-analyses and workshop are referred to, the papers in AJCN should be cited. In addition, the views expressed herein are those of the individual authors and/or their organisations, and do not necessarily reflect those of ILSI Europe.

KEY ABBREVIATIONS

AC	Available carbohydrate
CHD	Coronary heart disease
df	Degrees of freedom
ΔT	Difference treatment and control values
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
GI	Glycaemic index (of available carbohydrate, GI_{AC}; and of total carbohydrate, GI_T)
GL	Glycaemic load
HbA_{1c}	Glycated haemoglobin
HOMA	Homeostatic model assessment of:
	B beta-cell function
	S insulin sensitivity
	D disposition (combined effectiveness of B and S)
I^2	Fraction of total variance within and between studies due to Tau
IGT	Impaired glucose tolerance
k	Number of studies
MT	Mean of treatment and control values
P	Probability value (based on the z-score, |z|; based on Knapp & Hartung's standard error and the t-distribution, |kh-t|; based on the Monte Carlo permutations test, |mcp|; based on log-likelihood test, |Xbar|; based on Der Simonian and Laird estimate of between studies variance, Q)
REML	Relative maximum likelihood, which is a method of minimising residual errors around a mean or regression curve, i.e a method of fitting a mean or curve to a population of data
SE	Standard error (of estimation, of mean, of treatment difference according to context)
S	Severity of a condition (e.g. dysglycaemia, fasting blood glucose in excess of 5 mmol/L)

Tau	Among (or between) study error, and Tau^2 the between study variance
T1DM	Type-1 diabetes mellitus
T2DM	Type-2 diabetes mellitus
TG/FTG	Fasting plasma triglyceride
UC	Unavailable carbohydrate

CONTENTS

The following figures and table are placed in the main text (Book 1) or annexes (Book 2).

Methods:	*Figs 1 – 2*	*Table 1*
Macronutrient intakes:	*Figs 3 – 17*	*Tables 2 – 16*
Body weights	*Figs 18 – 20*	*Tables 17 – 19*
Fasting glucose	*Figs 21 – 31*	*Tables 20 – 30*
Glycated Proteins	*Figs 32 – 38*	*Tables 31– 32*
Fasting insulin	*Figs 39 – 40*	*Tables 33*
Insulin Sensitivity	*Figs 41 – 43*	*Tables 34 – 38*
HOMA scores	*Figs 44 –53*	*Tables 39 – 45*
Fasting triglycerides	*Figs 54 – 57*	*Tables 46 – 50*

Synopsis

Using systematic and meta-analytic methods, this report examines the scientific literature available prior to 2005 on **intervention studies** of "**glycaemic index**", extracting information on **macronutrient markers of nutrition, body weight** and **markers of health or health risk.** It was prepared as background information for discussion at the ILSI European Workshop on Glycaemic Response and Health, Nice, France 6-8 December 2006. The findings have relevance in respect of macronutrient intakes and related diseases, though specifically disease related to dysglycaemia. Persons interested are likely to be involved in clinical dietetics, diabetes associations, public health nutrition, nutrient requirements, the nutrition and health research community, food analysis, the food industry, the community of informed consumers, and food regulation.

The report has **dysglycaemia in focus** rather than dyslipidaemia, which may be secondary to dysglycaemia. **None of the studies reviewed investigate markers of tumour development**, though the observations have relevance in so much as certain cancers may associate with dysglycaemia. The studies available were mostly concerned with adults, though were too short in duration to record impact on **mortality** related to disease or nutritional state. Glycaemic response parameters of interest were glycaemic index, glycaemic load, available carbohydrate and unavailable carbohydrate; information about peak height of glycaemic response was too scant to analyse.

Improvement is found in one or more markers of health risk in free-living people of each health type examined when reduced glycaemic index or load diets of similar fat content are consumed. This applies to fasting blood glucose, glycated haemoglobin, fructosamine, insulin secretion, insulin sensitivity and people of each health type. Health types included are without diagnosed disease (healthy), at risk of disease (1° or 2° CHD), with diagnosed disease (type-1 and 2 diabetes), and people of normal, over, and obese weight for height. These effects of intervention and their statistical significance vary with circumstance.

While finding favourable health risk outcomes relate to **reduced glycaemic index** over all studies combined, and by health type, the analyses also show improvement relates importantly to **two roles for unavailable carbohydrate**. One is a reduction in glycaemic load due to replacement of available with unavailable carbohydrate (**g/g exchange**), and another is a presumed direct role of the unavailable carbohydrate. As a consequence, the **glycaemic index of total carbohydrate** is twice as precise as the glycaemic index of available carbohydrate when predicting **glycaemic load** while overall fat intake remains unchanged. The analyses show most marked reductions in glycaemic load associate with lower fasting triglycerides and body weight, but also **lower available carbohydrate intake**. The last is **without energy compensation** from higher intake of fat, and so **energy intake is lower**. Unexpectedly, there is evidence of potential harm due to inadequate efforts to achieve glycaemic index reduction in some studies. Such inadequacy is manifest by increases of carbohydrate intake, fasting triglycerides, and body weight. These tendencies are in an opposite direction to those intended.

Of particular interest to many are studies that show interventions with reduced **glycaemic load** diets result in both **reduced metabolisable energy intake** and a low rate of **body weight reduction.** This occurs when food intake is not tightly controlled and when glycaemic load reduction is by more than ~50 g glucose eq. per day. These effects appear sufficient to help with body weight maintenance and may help with compliance to caloric restriction. However, such intervention does not initiate rapid weight loss, which is no more than -2 to -10 kg per year (in the first year). A low dietary energy density might also cause weight loss and such an influence is not discounted in the present studies. However, across the intervention studies the **lower energy intake** most closely associates with **lower available carbohydrate intake** and **higher unavailable carbohydrate intake**, while there is unchanged fat intake.

The results of the present meta-analyses and meta-regressions agree well with related epidemiological studies emphasising glycaemic load and

unavailable carbohydrate (often indicated by 'fibre'), which can bring expectations of long-term benefits for everyone of every health group- whether healthy or with a dysglycaemic metabolic disease. There is evidence from the intervention studies that: The more *severe* the dysglycaemia (both fasting hyper- and moderate hypo-glycaemia) the greater is the impact of intervention with reduced glycaemic higher unavailable carbohydrate diets. Effects are generally *maintained over time* (≥12 weeks vs. <12 weeks treatment duration). *Normalisation* may be defined as low values being increased and high values being decreased without the phenomenon called 'regression to the mean', and such normalisation occurs with fasting blood glucose, insulin secretory function and sensitivity of tissues to insulin as assessed by HOMA scores. Thus normalisation occurs *even in people without diagnosed disease*. Among type-2 diabetic patients, those with the most impaired insulin secretion seem to normalise insulin secretory function poorly on the present dietary intervention. *Exogenous insulin* might then be needed for the low glycaemic higher unavailable carbohydrate diets to work most effectively towards overall improvement in glycaemic control, as with the improvement in type-1 diabetics treated with these diets.

It is strongly advised that consideration be given to revising the way that we express the potential of foods to affect long-term glycaemic control. This is because of the reasons identified, i.e. the role of available-unavailable carbohydrate exchange arising from food choices, the reduction in available carbohydrate intake uncompensated by fat, the improvement in precision of prediction of glycaemic load, and the evidence of potential harm due to inadequate attempts at glycaemic index reduction. Thus, due to the two roles of unavailable carbohydrate intake the intervention study outcomes collectively correspond to a *reduction in glycaemic load and elevation of unavailable carbohydrate intake more than to a reduction in glycaemic index of available carbohydrate*. As a minimum *requirement* for improving health, it is suggested that both glycaemic load and saturated fat are reduced to amounts less than commonly consumed by the majority of people in western populations; this while increasing or maintaining high unavailable carbohydrate consumption.

Introduction

The prevalence of non-communicable metabolic disease such as type-2 diabetes mellitus and coronary heart disease is high world wide (WHO/FAO 2003). Growth in the prevalence of diabetes and of risk factors for coronary heart disease suggests the eventual disease burden could overwhelm private and governmental health budgets (Turtle 2000; Pekka, Pirjo et al. 2002; Puska 2002; WHO/FAO 2003). Reduction of the glycaemic response to foods, via either reduced glycaemic index (Brand, Colagiuri et al. 1991) or reduced glycaemic load (Salmeron, Ascherio et al. 1997) has been proposed as a dietary means to help combat diabetes mellitus and possibly coronary heart disease (Liu, Willett et al. 2000; Kelly, Frost et al. 2004). Excessive glycaemic response to carbohydrate foods and low unavailable carbohydrate intake are implicated also in stroke (Oh, Hu et al. 2005) and certain forms of cancer, in particular colorectal cancer in some groups (Franceschi, Dal Maso et al. 2001; Giovannucci 2001).

Among early scientific enquiry is that of the Medical Research Council (McCance and Lawrence 1929) showing unavailable carbohydrate did not adversely elevate blood glucose concentrations and so was a useful source of carbohydrate energy for diabetics; available carbohydrate was seen as adverse or not well tolerated. That some available carbohydrate might also be suitable as an energy source for diabetics became evident later and was characterised as low glycaemic index available carbohydrate (Jenkins, Wolever et al. 1981). The idea that unavailable carbohydrate might have a direct or indirect role in glycaemic control is resurgent, with at least eight possible mechanisms proposed (Jenkins, Axelsen et al. 2000; Bjorck and Elmstahl 2003; Livesey 2003; Robertson, Currie et al. 2003; Hofman, van Drunen et al. 2004; Brennan 2005; Livesey 2005; Robertson, Bickerton et al. 2005; Ostman, Frid et al. 2006). Most recently a narrative review of replacement of ingredient available carbohydrate with ingredient unavailable carbohydrate suggests reductions in fasting blood glucose or glycated proteins in diabetics though not in individuals in whom fasting blood glucose is not raised (Livesey 2006). Among all these reports is consideration that for

optimal glycaemic control, unavailable carbohydrate might be used alongside low-glycaemic index available carbohydrate to limit the amount of high-glycaemic index carbohydrate amongst food choices. However, the relative importance of unavailable carbohydrate and low-glycaemic available carbohydrate in health promotion and management is unknown.

Objectives

The objective was to construct a database of randomised controlled (or similar) intervention studies to address queries about the possible role of glycaemic load and indices of glycaemic load, as modifiable by available and unavailable carbohydrate, in the management of health and prevention of disease in respect of common metabolic conditions.

Queries addressed were about health types, mortality, risk factors (biochemical, constitutional and dietary), and about duration of treatment. Each is described briefly here and in more detail further below.

Health types were to represent groups of people ostensibly:

> -in good health
>
> -with impaired glucose tolerance
>
> -with type-1 diabetes mellitus
>
> -with type-2 diabetes mellitus
>
> -with or at risk of coronary heart disease.

Participant groups were also classified as normal, overweight and obese for combined health types.

Biochemical risk factors were:

- fasting blood glucose,
- fasting insulin,
- glycated proteins (HbA$_{1c}$ and fructosamine and these combined),
- insulin sensitivity
- calculated HOMA %S,
- pancreatic B-cell function calculated as HOMA %B, and HOMA %D
- plasma triglycerides.

Body weight was the only constitutional risk factor addressed. Dietary risk or nutritional factors were metabolisable energy, fat, available carbohydrate, unavailable carbohydrate, and protein intake, together with potential risk factors glycaemic load, and various indices of glycaemic load. Duration of treatment was either as a continuous variable, or by treatment duration <12 weeks or greater than ≥12 weeks. An adjustment for risk factor half-life was examined where treatment duration was inadequate to reach steady state observations.

The primary question addressed is:

Does a diet with a reduced glycaemic load achieved without changes in fat and protein intake reduce total mortality or any one risk factor for disease, either according to health type or for all types combined?

The secondary question addressed is: Among glycaemic load, glycaemic index of available carbohydrate, glycaemic index of total carbohydrate, and peak height of carbohydrate, which associates, or most associates, with reduced risk to health or mortality?

The tertiary question, as usually implied, is to uncover any related adverse effects.

METHODS

Inclusion and exclusion protocol

Data were selected in four processes applied sequentially:

   i.   Literature search

   ii. Scan of title and abstract

   iii. Review of full paper

   iv. Database query

Those related to database queries are described with the results; those resulting in inclusion of data in an intervention database are described below.

Literature search

Electronic databases were searched including the Cumulative Index to Nursing & Allied Health Literature (CINAHL) from 1982 to Jan 2005, the Cochrane Central Register of Controlled Trials (CENTRAL) to Jan 2005, Elsevier Medical Database (EMBASE) from 1980 to Dec 2003, the U.S. National Library of Medicine database (MEDLINE via the PubMed portal) from 1950 to Jan 2005; Elsevier's Science-Specific Search Engine on the Internet (SCIRUS) to Jan 2005 and Blackwell's Nutrition and Food Science database underpinned by the Commonwealth Agricultural Bureau International (CABI) from 1981 to Jan 2005. An all "field" search for "glyc(a)emic index" or "glyc(a)emic indices" or "glyc(a)emic load" alone and each together with "diabetes" was performed. See **Annex 1** for additional info on literature search.

PubMed had records on all the intervention studies included in the present analyses with exception of two study reports unpublished prior to 2005. Analysis of the number of studies appearing year on year shows a steady increase in numbers **(Fig 1)** from one record in 1960, to 2772 records (without duplication) by Jan 2005, with the maximum yearly rate in 2004 being 398 records without duplication. A high level of untargeted records arose because glycaemic index is related to diabetological measures in addition to being a food or diet characteristic, and for other reasons (see **Annex 2** for more information on excluded studies).
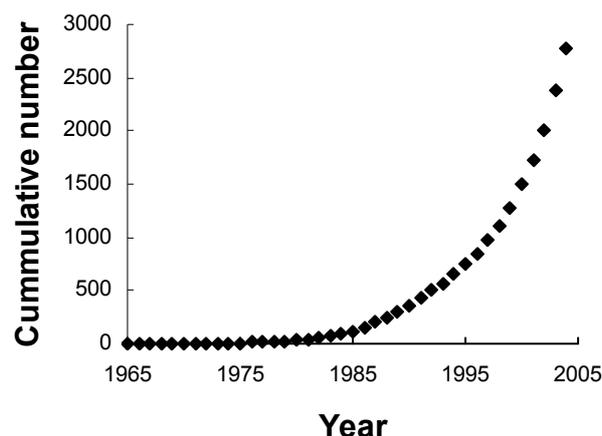
Fig 1: Cumulative number of records retrieved without duplication that match all fields for "glyc(a)emic index" or "glycaemic indices" or " glycaemic load" from e-databases, CABI, CINAHL, CENTRAL, EMBASE, MEDLINE, and SCIRUS.

Preliminary selection from titles and abstracts

Scanning of the titles and abstracts present in the electronic records enabled identification of potentially relevant studies. The basis for inclusion or exclusion at this stage were:

Inclusions when scanning titles and abstract:

i)   Publications in which glycaemic index or load referred to foods or diets and not to a diabetological parameter.
ii)   Controlled intervention studies.
iii)   Duration of treatment >1 week.
iv)   Studies in healthy people, people with either impaired glucose tolerance or hyperlipidaemia or at risk of coronary heart disease or having diagnosed type-1 or 2 diabetes.

Exclusions when scanning titles and abstract:

v)   Epidemiological studies
vi)   Interventions to assess impact on any form of cancer.
vii)   Interventions in animal studies.
viii)   Interventions with a historical design.
ix)   Studies clearly without a control treatment.
x)   Treatments targeting the use of unavailable carbohydrate, protein, or fat in place of total or available carbohydrate in the absence of the targeting of a reduction in glycaemic index of available carbohydrate.
xi)   Treatments reducing glycaemic index of the diet using inhibitors of carbohydrate digestion.

xii) Change in glycaemic index or load as part of a multiple intervention not reflected in the control treatment, such as with drugs or lifestyle factors.
xiii) Interventions specifically to study satiety, which had no relevant outcomes.
xiv) Publications related to food product characteristics, including determinations of glycaemic index or load.
xv) Methodological publications.
xvi) Publications related to exercise performance.
xvii) Publications on guidelines, reviews, commentaries and abstracts.
xviii) Study proposals, commentaries and reviews.

At closure of the register a number of studies were known to be ongoing (see **Annex 1(2)** for more about the ongoing studies).

Examination of full papers

Where titles and abstracts together with the above criteria indicated potentially relevant studies, the full papers (64) were obtained for more detailed assessment, these together with reviews to asses whether there might be any other studies not so far encountered.

Included studies

Studies were included only if they met the above criteria and outcome data could be extracted and were from English language publications prior to 2005 (42 publications) or from a foreign language with English abstract in which additional information could be sought from the authors (1 publication) or from unpublished work available by that time and subsequently published (2 reports). Due to some publications reporting more than one study, there being repeat observations (across the duration of treatment) in some studies, and some outcomes being assessed by more than one method, the 45 publications yielded 88 rows of effect estimates contrasting "high vs. low GI diets". During analysis, intermediate time points were included whenever duration of treatment was an independent continuous variable or when an overview of the total evidence was sought, otherwise intermediate times were excluded.

Study types and numbers

All studies included had control vs. treatment comparisons and designs were either crossover or parallel or control-treatment-control (19, 25 and 1 respectively). **Annex 3** provides details of the randomisation procedures.

Participant types and number

The database includes participants of various ages (group mean ages 10 to 63 years) with both males (511) and females (461). Participants were either normal weight (16 studies), overweight (18 studies) or obese (10 studies) or unclassified by weight (one study). Similar numbers of participants took part in the treatment arms (770 on high GI treatment and 793 on low GI treatment). Study participant were either healthy i.e. no diagnosis of disease was evident (13 studies) or had impaired glucose tolerance (2 studies, duration of impairment unknown) or had type-1 diabetes (7 studies, mean duration from diagnosis 3 to 16 y, one unknown duration) or had type-2 diabetes (17 studies, mean duration from diagnosis ~0 to 12.5 y, seven unknown duration) or were at risk of primary CHD (4 studies, duration unknown) or secondary CHD (1 study, duration unknown) or had hyperlipidaemia (1 study combining Type II a, Type II b, Type III, mean duration from diagnosis 4.7 y). Studies included participants on medication. Insulin dosage was reported in all seven studies with type-1 diabetics, two of 17 studies with type-2 diabetics and in one of one study with participants at risk of secondary CHD. All but one study with type-2 diabetics received non-insulin medication for glycaemic control (hypoglycaemic agents).

Intervention types and numbers

Interventions were by diet, with intention to exchange the form of available carbohydrate (high vs. low glycaemic index). The extent to which this was achieved varied between studies. Moreover, in many cases the dietary changes were accompanied also by variably higher quantities of unavailable carbohydrate (to be discussed later in the report). Thus the diets are sometimes qualified collectively herein as: variably lower glycaemic and variably higher unavailable carbohydrate. Diets were achieved either via providing advice (with support of a dietician and food lists) (24 studies) or by

providing some or all foods to be consumed (21 studies, two of which were largely advisory). Intentionally the treatments had been to achieve exchanges of available carbohydrate while maintaining similar amounts of other macronutrients, though variable differences in energy and other macronutrient intakes are found in the present analysis (discussed). To facilitate queries on intervention duration, and queries on adjustments of outcomes for *prior estimates* of turnover times for glycated proteins (HbA$_{1c}$ and fructosamine), studies were the database with treatment durations from 1.5 to 52 weeks. Studies included interventions with food exchanges at one or two or three (or more) or probably three (or more) meals per day (6, 2, 25, and 12 studies respectively). This was to facilitate queries over meal numbers and 'dose' dependency of outcomes in relation to dietary glycaemic load or any of its indices. Diets had been intended to meet maintenance and growth requirements (37 studies) or sub-maintenance requirements (8 studies); no overfeeding studies were encountered. Control over food intake was classified as ad-libitum (7 studies), limited controlled food intake (22 studies) and controlled food intake (16 studies).

Intervention settings and locations

All studies were in free-living people. Thus no studies were of hospitalised patients or subjects housed in metabolic wards or centres of human nutrition. For more information see **Annex 4**.

Studies are represented from all continents: Asia (4 studies), Australasia (6 studies), Europe (19 studies), South America (2 studies), Africa (1 study), North America (13 studies).

Measurement types

Mortality and morbidity scores were not collected as few studies were of sufficient duration to encounter reliable responses. No data were reported on mortality, cardiovascular events or diabetic complications. Hypoglycaemia was reported by some. Changes in the severity of risk factors were the primary outcomes: fasting glucose, glycated proteins (HbA$_{1c}$, fructosamine), fasting insulin, insulin sensitivity, calculated HOMA %S, calculated HOMA %B, calculated HOMA %D, fasting plasma or serum triglycerides, and body

weight. Data on fasting total, HDL and LDL cholesterol were extracted but not analysed. Other outcomes were: macronutrient intakes, physical activity and **adverse events**. Insufficient numbers of studies monitored physical activity, three that did so provided no data (Kiens and Richter 1996; Kabir, Oppert et al. 2002; Brynes, Mark Edwards et al. 2003). The following intake data were noted:

- Metabolisable energy intake (41 studies, 26 with freedom to respond: the other 15 had controlled food intake),
- Available carbohydrate intake (41 studies, 26 with freedom to respond),
- Unavailable carbohydrate intake (36 studies, 22 with freedom to respond),
- Protein intake (39 studies, 24 with freedom to respond),
- Fat intake (40 studies, 26 with freedom to respond),
- Calculated glycaemic load (38 studies, 14 with 'fixed' intakes due to intervention and 24 with freedom to respond differently),
- Dietary glycaemic index (% glucose as reference) ostensibly of available carbohydrate (41 studies, 15 with 'fixed' intakes due to intervention and 26 with freedom to respond differently),
- Calculated glycaemic index of total carbohydrate (35 studies, 13 with fixed intakes due to intervention and 22 with freedom to respond differently).

Study quality

Study quality was based on criteria in the Cochrane Reviewers Handbook (Section 4.1.6). See **Annex 5** for more information on study quality. Because all studies had a similar quality score, the data were analysed without weighting for study quality.

Dropouts

Information on participants dropping out of studies either themselves or for being non-compliant was available for 44 of the 45 included studies. Dropouts ranged from zero to 61% of study entrants with a mean of 8% or 16% after weighting for the number of participants entering a study. See **Annex 6** for more information on dropouts.

Intention to treat and compliant to diet

Twenty-five studies reported outcomes that were considered intention to treat analyses, while 21 reported outcomes on the basis of compliant to treatment analyses. Combining of information from these studies was therefore considered the results of compliant to diet analysis. In the study reporting both intention to treat and compliant to treatment analysis (Giacco, Parillo et al. 2000), data were therefore extracted from the latter analysis for inclusion in the database.

Participant numbers and power calculations

The number of contrasts (units) per study is the number of participants per treatment arm. These were generally small: there were 15 studies with ≤10 unit contrasts, 15 studies with >10 to ≤20 unit contrasts, 11 studies with >20 to ≤30 unit contrasts, and 4 studies with >30 to <60 unit contrasts. Power calculations were seldom given, and then only for a limited number of measurements made.

Confounding factors

It was considered that differences in macronutrient intake between treatments might confound the interpretation of effects as due to glycaemic index. Although many studies report designs intended to have similar macronutrient intakes in the treatment and control arms, the precision with which this is achieved varies between studies. The possibility that difference in treatment outcomes covary with unintended differences in macronutrient intakes is examined.

Included study citations

Included studies are cited in **Annex 7** by health type. Health types were assigned by authors of the original publications and reports. The use of the health types here should not be implied to say that particular participants fit a health type uniquely. For example, all those with diabetes might also be considered at risk of coronary heart disease. Likewise those 'healthy' individuals who are overweight or obese might be considered at risk of diabetes (a category not defined here). However, the analyses undertaken consider a) each outcome in each health type separately, b) each outcome across all studies combined – regarding the health markers to vary continuously independently of health type, and c) all studies recombined by other types (e.g. normal weight, overweight, obese). **See Annex 7** for more information on health types.

Duplicate information

Different aspects of studies reported in separate publications were combined as one study: See **Annex 8** for more information.

Data extraction

Numeric and alphanumeric (string) information were initially extracted by G. Livesey who created a provisional database in Excel with fields as described below. A copy of the provisional database was made with empty 'fields'. The fields in the empty copy were completed by R Taylor who independently extracted data from the source publications. Inequalities in the content of cells in the two provisional databases were labelled computationally as 'FALSE' and examined by both RT and GL to make corrections. Where inconsistencies remained, agreement was reached by joint consultation of the publication (or report) of the study in question. The agreed provisional data was imported and stored in a StataCorp (Texas) Stata SE 9.0 database file (*.dta) for query and analysis. This procedure allowed independent extraction to an identical format in which differences in extraction could be identified systematically and computationally, and data could be transferred seamlessly to a Stata database for storage and analysis without risk of copy (input) errors. Conversion of data in reported units to common SI units, where necessary,

were made while extracting data into Excel in each of the two provisional databases.

Extracted data counts

Data extracted into the intervention database used one study condition per row (number of rows = 88), and one field per column (number of columns = 505). The total number of database cells used was 44,440 filled at a density of 29%.

Database fields

The fields of information collected for each higher vs. lower GI diet contrast are given in **Annex 9**

Study identities

The identity of studies is expanded on in **Annex 10** as these are used at present to identify the source of information in text, table footnotes, and graphs.

Conversion factors

Glycaemic index as % glucose was 1.43 times the index as % bread (Foster-Powell and Miller 1995). To obtain SI units: Fasting glucose, 18.02 mmol/l per 1 mg per dl; fasting insulin, 0.143 pmol/ml per 1 µU/ml; triglyceride (triacylglycerol) 88.5 mmol/l per 1 mg/dl (Rowlet 2005). Also fasting capillary blood glucose = -0.61 + 0.94 x fasting venous glucose (Colagiuri, Sandbaek et al. 2003). Food energy conversion factors used to convert energy (% Metabolisable Energy) values to weights (g) were 4.184 kJ per 1 kcal; protein, 16.7 kJ per 1 g; available carbohydrate, 16.7 kJ per 1 g; fat, 37.7 kJ per 1 g; unavailable carbohydrate 8 kJ per 1 g (Livesey 1990).

Statistical analysis

Random effects meta-analyses and meta-regressions, each weighted by inverse variance, were undertaken using *meta* and *metareg* in Stata 9.2 SE (StataCorp, Texas) according to Cochran guidelines (Deeks J, Higgins J et al.

2002). *Meta* provides a combined mean with 95% confidence intervals, the Der Simonian and Laird estimate of between studies variance (DSL), Q-test for heterogeneity, and an asymptotic z-test for the null hypothesis that the true effect is zero. *Metareg* was (unless stated otherwise) executed using a relative maximum likelihood approach (REML) that provided regression coefficients with standard errors, Knapp & Hartung's t-test of significance, likelihood-ratio estimates of between studies variance (Tau^2), a likelihood-ratio test for heterogeneity equal to zero and an expression of the proportion of total variation due to heterogeneity (I^2). Optionally when the regression model included a constant the Monte-Carlo permutations test (*permut*) was used to assess whether a regression coefficient differed significantly from zero.

Mean differences between dietary treatments were expressed either in absolute units when the metric was common to all studies or as a percentage of the average of the mean dietary treatments when metrics differed among studies.

Parallel and crossover studies reporting no crossover effects were combined (see below). Studies generally reported either treatment difference in end measurements or difference in change with time (change score) for each treatment or both. Where a standard error difference between treatments in end measurements or change in measurements in time were not reported by authors of the reviewed publications they were calculated from either confidence intervals or P-values, error degrees of freedom, the number of multiple treatment comparisons reported, and the method for testing the significance of difference (Students' paired-t, Tukeys etc). Studies very often did not report either the dependent (unpaired) or the independent (paired) standard error difference between treatments. Independent standard error differences between treatments were therefore recalculated and used with coefficients of correlation (r_p) to estimate the dependent standard error differences. See **Annex 11** for information on how the dependent standard error was estimated.

Values of $\sqrt{1-r_p}$ derived at present are given in **Table 1** in **Annex 11**. An assumption in **Annex 11** is that $\sigma_1 \cong \sigma_2$ is valid for the present studies. An

assumption of equality of r_p from study to study is nevertheless approximate and often varies with duration of treatment (see the standard errors in **Table 1** in **Annex 11**). Future studies need to provide information about $SED_{dependent}$ as is done in most clinical studies examining drug treatment effects.

Calculation of differences of mean treatment effect and the independent standard errors of difference in treatment effects for each study was possible via a number of different routes depending on the information available. Accuracy of a method and availability of information for the method dictated preferences. For mean treatment difference values the preference was m1>m2>m3>m4.

- Method **m1** was the reported treatment difference (where in parallel studies it had already been adjusted for difference in start mean values between dietary treatment groups).
- Method **m2** was the treatment difference calculated from reported change scores.
- Method **m3** was the treatment difference calculated as the difference in change scores calculated from reported start and end values for each treatment.
- Method **m4** was the difference in reported end values for each treatment (note, parallel studies without start values were excluded from the database).

Standard error differences between treatments also took on methods preferences, sed1>sed2>sed3>sed4.
- The standard error difference **sed1** was the reported (extracted) value.
- The **sed2** was calculated from change score standard errors (pooled standard error differences across time within study).
- The **sed3** was estimated from the pooled independent standard error difference between end scores and Eq. 8 or 9 in **Annex 11(1)**; in these equations the independent standard error differences were calculated from the number of observations per mean and the mean's standard deviation.

Standard deviations for start and end mean values also took on preferences; these were in the order sd1>sd2>sd3. Standard deviation sd1 were as

reported (extracted from studies), while sd2 were calculated from standard error means and the number of observations per mean. Standard deviations sd3 were estimates obtained for instances where neither sd1 nor sd2 were available, and were imputed from first or second order regressions between sd1 and the reported (extracted) mean using observations from studies that imparted this information.

This procedure was elaborated to maximise precision and minimise bias for combined study treatment effects and was essential to retaining the maximum number of studies in the analysis. Doing so avoided bias (estimable) from dropping studies with incompletely reported statistics but included bias (not estimable) due to estimation of sd3, and so sed3. The consequence of the latter for the random effects analyses used is less than would be expected for fixed effect analysis.

The influence statistic and outliers

The influence a perceived outllying study on a summary mean or trend can be expressed as the 'influence statistic ($\Delta\hat{\beta}ij$)' which is change in mean or trend due to deleting the study when divided by the standard error of the mean or trend after deletion. See **Annex 12** for more information.

Interpretation of meta-analyses

The objective of meta-analyses (such as *meta*) is to combine observations from a minimum of three studies (2 degrees of freedom) in order to improve accuracy, precision and power of observation and to provide an overall combined estimate of the statistical significance of a result (Deeks J, Higgins J et al. 2002). While meta-regression (such as *metareg*) can theoretically be applied to as little as three studies, caution is advised in the interpretation of results when there are less than ten studies (or less than 8 degrees of freedom)(Deeks J, Higgins J et al. 2002). Two independent sets of meta-regressions each with six studies that reach a similar conclusion yields more convincing evidence.

P values are given for combined means and regression coefficients. The P values are given in two ways. Firstly they are as given by *meta* and

metareg. A person coming to the report with only one particular question (one that is asked prior to viewing the report and that is answered herein alongside many others) would use this P value to assess the significance of the result for them. In other instances the P value is preceded by a number. This indicates a Bonferroni adjusted P value is given to account for multiple comparisons e.g. division of all studies into different categories by health type. The number preceding the P indicates the number of multiple comparisons made, which is the number of health categories assessed (vs. $\mu = 0$). The Bonferroni adjustment offers conservative estimates for multiple comparisons. When a new set of multiple comparisons is made by distributing the same data in a different way, e.g. division of all the studies into different categories by body weight class, the Bonferroni adjustment then uses the new number of multiple comparisons. This ignores the fact that prior multiple comparisons have been drawn from the data. The new multiple P is appropriate however for a person coming to the report asking a specific question about any such comparisons among any one set of categories (in this example either health or body weight class).

Definitions

The definitions used in this review are given below and are based on those of WHO/FAO (WHO/FAO 1998; FAO 2003) and others as follows. Recognition is given to alternative suggestions from an ILSI Europe working group on glycaemic index methodology (Brouns, Bjorck et al. 2005), and from individual research groups (Monro 2003; Anfinsen, Wolver et al. 2004). The interrelationship between the various definitions is as outlined previously (Livesey 2005a). The definitions given are abstract in that deviations occur in practice, as noted previously (Foster-Powell, Holt et al. 2002) and as outlined below.

The relationship of one definition to another is outlined in **Fig 2**.
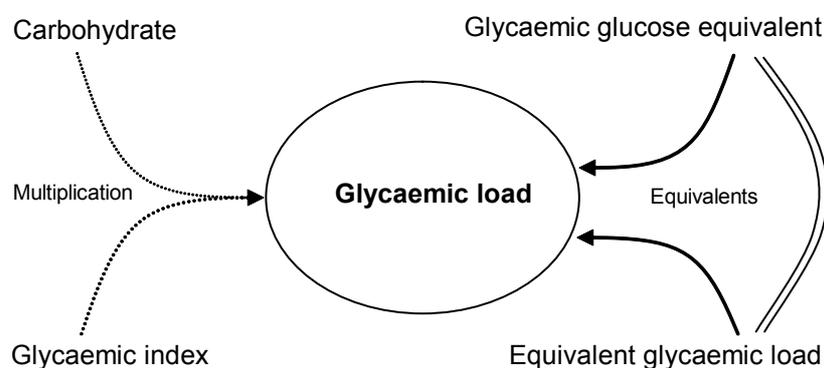
Fig 2: Terminology conceived regarding glycaemic response and health. Based on Livesey, 2005, this diagram emphasises the issue conceptually with glycaemic load at its centre surrounded by thee methods of determination. A calculation method measures available (or total) carbohydrate and glycaemic index of available (or total) carbohydrate respectively and multiplies these together. Glycaemic glucose equivalent and equivalent glycaemic load are direct methods of measurement. Although conceptually related, the methods are not identical in practice due to methodological issues and non-linearity of the glycaemic response with dose.

Summary of Glycaemic Response related definitions

Available carbohydrate is the total carbohydrate in food that is absorbed and used in post-absorptive carbohydrate metabolism. (Abbreviation AC. Units: g, etc.)

Unavailable carbohydrate is the total carbohydrate in food that is not absorbed in the small intestine, some of which may be fermented in the colon. (Abbreviation UC. Units: g, etc.) In most studies unavailable carbohydrate is equivalent or close to the amount of fibre (inclusive of all resistant carbohydrates to the extent measured). However, stress is placed here on the unavailablility of carbohydrate as glucose when used in place of available carbohydrate (McCance and Lawrence 1929; Livesey 2005a), the several other mechanisms by which this unavailability may act (Livesey 2005b)

including its presence and effects as a fermentable carbohydrate in the colon (Robertson, Livesey et al. 1999; Robertson, Livesey et al. 2000; Robertson, Currie et al. 2003; Robertson, Bickerton et al. 2005), and which some have called 'the second meal effect' (Bjorck and Elmstahl 2003). It is these that are considered relevant here rather than the associated substance in fibre or high fibre food that is sometimes inferred by 'fibre'.

Glycaemic Index of available carbohydrate: is the impact of a food containing 50g available carbohydrate, when fed alone with water, on the glycaemic response expressed as the 2-h incremental area under the blood glucose curve and expressed as a percentage (indexed) to a similar amount of oral glucose. (Abbreviation GI_{AC}. Units: %glucose meaning g glucose eq. /100 g available carbohydrate.)

Glycaemic Index of total carbohydrate is the impact of a food containing 50g total carbohydrate, when fed alone with usually water, on the glycaemic response expressed as the 2-h incremental area under the blood glucose curve and expressed as a percentage (indexed) to a similar amount of oral glucose. (Units: %glucose, meaning g glucose eq. /100 g total carbohydrate.) This measurement is often used when a product has no or limited amounts of available carbohydrates and is sometimes called the relative glycaemic index. (Abbreviation GI_T. Units: %glucose meaning g.glucose eq. /100 g total carbohydrate.)

Glycaemic Load is either *I* or *II* as they are equivalent (Abbreviation GL. Units: g glucose eq.):

I: the sum of products for the glycaemic index of the available carbohydrate and the available carbohydrate content of food or ingredients comprising a food, meal or diet, which can be summarised as $\Sigma (GI_{AC} \times AC)/100$.

II: the sum of products for the glycaemic index of total carbohydrate and the total carbohydrate contained in foods and ingredients comprising a food, meal or diet, which can be summarised as $\Sigma (GI_T \times TC)/100$.

Glycaemic glucose equivalent is the amount of glucose having the same glycaemic impact as a given amount of food. (Abbreviation GGE. Units: g glucose eq. etc.)

Equivalent glucose load*, which correlates with a glycaemic response index*, is approximately the weight of glucose having the equivalent glycaemic response as a given amount of food. (Units: g,)

Aglycaemic available carbohydrate is invented here to indicate the difference between available carbohydrate intake and glycaemic load (AC-GL). Potentially, this quantity allows a change in emphasis during communications from 'eat a lower glycaemic load diet' which might be wrongly interpreted as 'consume more fat', to emphasise "eat more aglycaemic carbohydrate", which seems less likely to be interpreted as eat more dietary fat. In addition, usually high glycaemic load and unavailable carbohydrate have directionally opposing influences on health markers and so are not additive, while aglycaemic carbohydrate and unavailable carbohydrate have directionally similar influences and are additive.

Total aglycaemic carbohydrate, is the sum of aglycaemic available carbohydrate and unavailable carbohydrate (non-glycaemic carbohydrate)

Glycation index, is a quotient introduced here on the basis that glycaemic load and dietary fat may be determinants of protein glycation. Somewhat arbitrarily it is the sum weight of GL and fat intake divided by the weight of protein, fat, available and unavailable carbohydrate intake.

* Items marked with an asterisk are defined by patent application and not used further in this review.

Modes of expression: The units given for the quantities defined above may be 'as is' or as a rate per unit food or meal or diet (e.g. per portion size, per 100 g food, per 100 ml drink etc. per meal, per 2000 kJ diet etc) or per unit duration (e.g. per day, per week) and per person (etc).

Inferences from the definitions: The definitions applied in this review stand alone on their own merit. Measures of glycamic response do not inform about other nutrients or nutritional properties. Potential confounding by other nutrients is examined were possible. Information about dietary energy density is not available in most studies. A question of whether dietary energy density is confounded by glycaemic response or visa versa is therefore not open to assessment at the present time.

Practical realities

The definitions of glycaemic index/load are not exact descriptions of qualities and quantities measured in foods. In practice published values, such as tabulated in the International Tables of Glycaemic Index and Glycaemic Load are sometimes based on total carbohydrate rather than available carbohydrate. Some food tables give carbohydrate as total carbohydrate, which has then occasionally defined the portion size taken for GI determination. Some studies apply information on GI values derived in these different ways to total carbohydrate and some to available carbohydrate. Even when available carbohydrate is used or implied, it may be based on different quantities, for example available carbohydrate as monosaccharide equivalents or available carbohydrate by difference (or weight as is). In some cases the amount of available or unavailable carbohydrate in a food tested for its GI value has not been analysed but has been assumed from food tables. In other studies the portion size has been estimated on the available carbohydrate content prior to processing and processing has increased the resistant carbohydrate content. However, for the present purpose, the definitions of GI and GL are considered as though exact.

RESULTS

See **Annex 13** for the conventions used in figures and tables.

Macronutrient intakes

Preamble

Prior to 2005, 40 relevant studies were available reporting macronutrient intakes following intervention to change from high to low glycaemic carbohydrate (variable high unavailable carbohydrate) diets. Of these 38 reported GI values (or information on foods to estimate GI). Among these studies, observations were from healthy (k = 10) or glucose intolerant (k = 1) or type-1 (k = 6) and type-2 (k = 15) diabetics or subjects at risk of primary or secondary coronary heart disease (k = 5), and a hyperlipidaemic (mixed categories, k = 1) group of people. No studies provided observations repeated at different points in time.

Macronutrients

For analysis here the studies are either combined or divided to extreme categories according to whether foods are available ad libitum or available in controlled amounts, or an intermediate category where there is limited (or partial) control over food intake. In the **ad libitum** category, food intake could vary but diet composition was fixed (food was provided or largely provided). In the intermediate **limited controlled** category, scope existed for both intakes and composition to vary (the diet was advised or largely advised). In the **controlled** food intake category, both food intake and composition were fixed (food was provided or largely provided and may have been adjusted in amount if body weight changed). Inequalities other than due to GI between treatment and control diets could arise in all three food intake categories according to the food choices and application of the dietary prescription.

It is customary to examine **correlations** between principal determinants of health investigated and other possible determinates. In the present case the principal determinants investigated are the glycaemic load

(or some derivative of glycaemic load such as the glycaemic index) and unavailable carbohydrate. A simple table of correlations between all potential macronutrient determinates and indices is **inadequate** in the presented interventional studies because differences from zero achieved in glycaemic load or index or unavailable carbohydrate intake are not accompanied by simple monotonic or unidirectional increases or decreases in other variables. However, associations may show a rise or jump in direction (affecting a constant) then follow a monotonic trend (affecting a slope). The **jump** may be in a direction opposing the linear **trend** (a bidirectional or bitonic response). Both the jump and the linear trend are assessable by inverse-variance random effects REML linear regression.

Macronutrients in relation to Glycaemic Index

Among studies of GI, difference between low and high glycaemic treatments result in different intakes of metabolisable energy, protein and available carbohydrate that tend to rise or jump upwards initially then fall as the glycaemic index falls. This appears most evident for available carbohydrate and for all these macronutrients in the ad libitum category - see **Figs 3** to **6** (3 and 5 here, and 4 and 6 in Annexes 17 and 18) and corresponding **Tables 2** and **3** here, and **4(1)** and **4(2)** in **Annexes 17** and **18**. In these instances the jump did not reach statistical significance (nul hypothesis: REML regression constant equal to zero at zero difference in glycaemic index). However, the constants are positive in all three food intake categories for each of energy (48 to 1009 kJ/d), protein (1.5 to 15.6 g/d), and carbohydrate (14.8 to 34.6 g/d), but not for fat (-8.3 to 7.9 g/d), suggesting that the interventions elevate the amounts of these components that are ingested, with this being reversed progressively when diets have particularly low glycaemic carbohydrate.
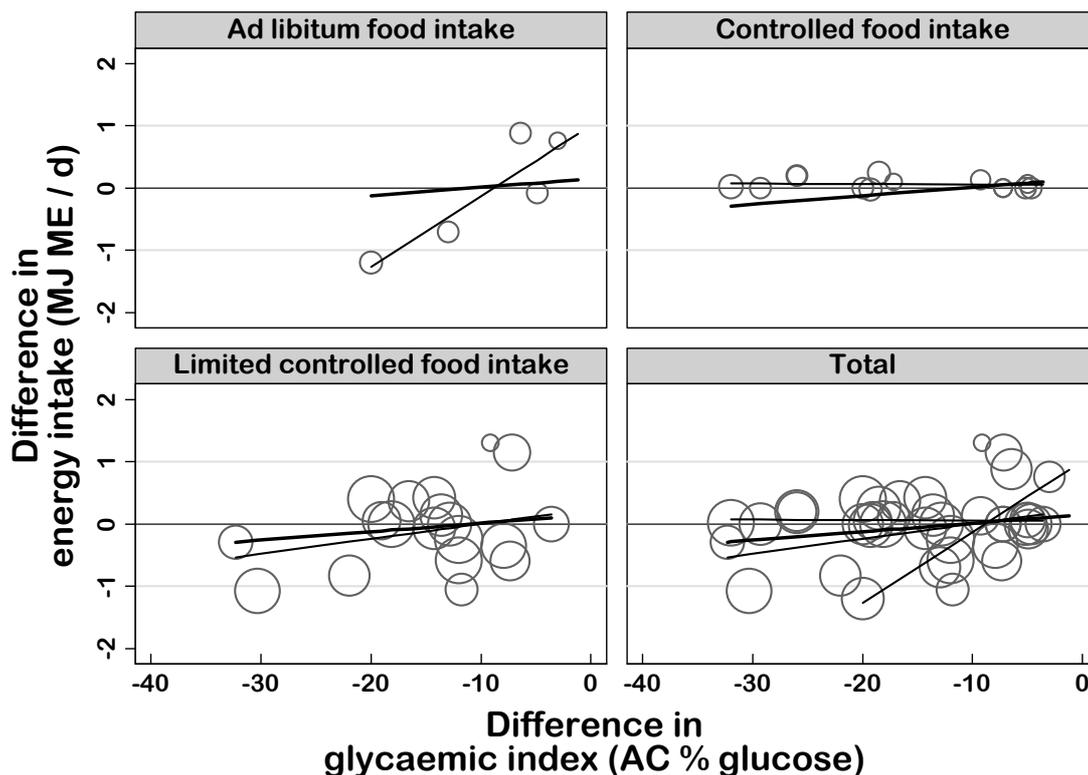
Fig 3: Difference in energy intake associated with difference in glycaemic index achieved, by food intake category (narrow line) and all studies (total bold line). In each panel, imprecise studies are indicated with small bubbles) (See **Annex 14** for details on statistics and sources/references.)

TABLE 2: *Difference in metabolisable energy intakes in intervention studies related to difference in glycaemic index$_{ac}$ achieved, by category of food intake control. (Statistical details in* **Annex 15***.)*

	All studies combined	Control	Limited control	Ad libitum
k (df)	38 (36)	14 (12)	19 (17)	5 (3)
Slope (kJ/GI%glu)	13.5	-0.8	24	113
SEE	9.7	0.6	16	37
P>|kh-t|	0.17	0.9	0.2	0.005
3P	-	**>0.99**	**0.6**	**0.015**
Constant (kJ/d)	150	48	244	1009
SEE	170	148	302	445
P>|kh-t|	0.38	0.75	0.47	0.11
3P	-	**>0.99**	**>0.99**	**0.33**
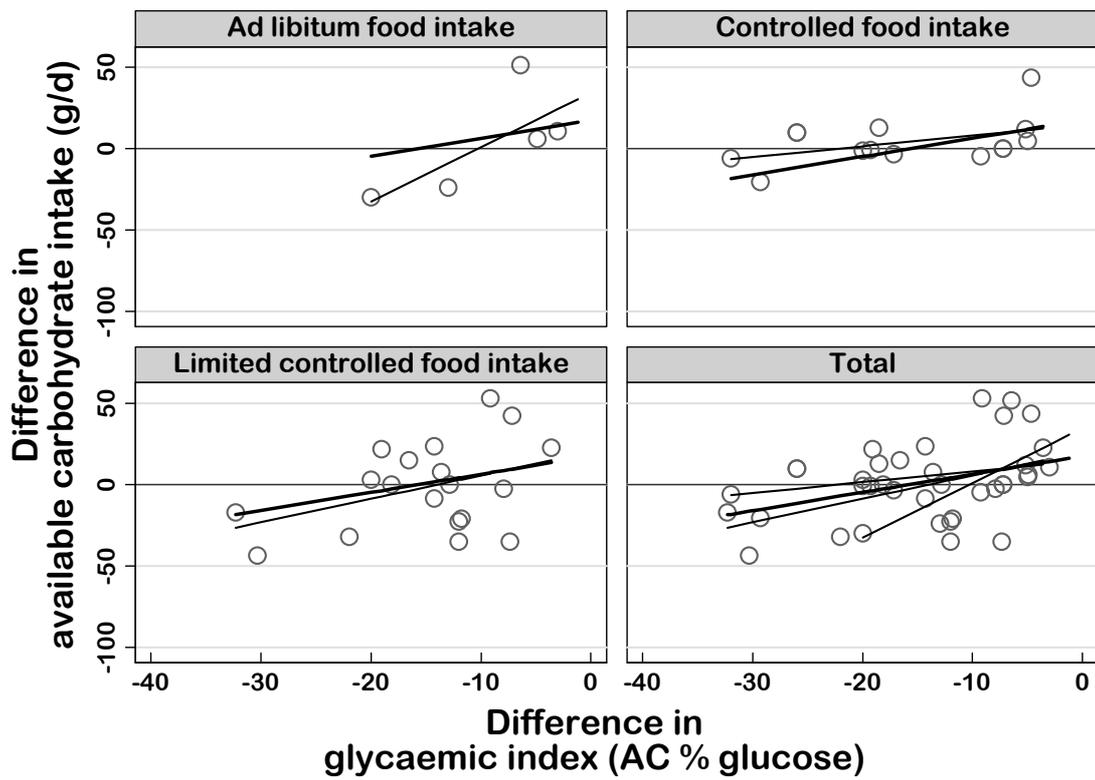
Fig 5: Difference in the intake of available carbohydrate associated with difference in glycaemic index achieved. (See **Annex 14** for details on statistics and sources/references.) (Bubbles of similar size are indicative of similar variances (SE^2+Tau^2) for each study, often due to random effects ($Tau^2>0$) as in this instance ($Tau^2>>SE^2$).

TABLE 3: *Difference in available carbohydrate intakes in intervention studies related to difference in glycaemic index$_{ac}$ achieved, by food intake control (see* **Annex 16** *for more statistical details).*

	All studies combined	Control	Limited control	Ad libitum
k (df)	38 (36)	14 (12)	19 (17)	5 (3)
Slope (g/GI%glu)	1.12	0.66	1.44	3.35
SEE	0.43	0.39	0.80	1.87
P>|kh-t|	0.013	0.11	0.09	0.17
3P	-	**0.33**	**0.27**	**0.51**
Constant (g/d)	17.6	14.8	20.2	34.6
SEE	7.2	7.2	13.4	21.3
P>|kh-t|	0.021	0.063	0.15	0.20
3P	-	**0.189**	**0.45**	**0.60**

Fat intake is essentially unchanged as the difference in glycaemic index expands, though not excluded in the ad libitum category is a falling trend in fat intake following an initial upwards jump. (See **Figs 4 & 6** and **Table 4** in **Annex 18** for effects on protein and intake.)

Intakes of unavailable carbohydrate are often variably higher on taking the lower glycaemic diets in all intake categories. (See **Fig 7** and **Table 5** in **Annex 19** for effects on unavailable carbohydrate intake). However, there is no trend as in the case of energy, protein or available carbohydrate. Random effects meta-analysis shows increase of unavailable carbohydrate intake to be significant over all studies combined at +6 (95% CI 3 to 11) g unavailable carbohydrate per day (P>\|z\| = 0.007) with significant random effects (Q = 3715, 35 df P>Q <0.001) and a Der Simonian and Laird estimate of between studies variance of 185 (g per day)^2 or 13 g/d.

Glycaemic Load in relation to Glycaemic Indices

A fall in glycaemic load is evident that is 'dose' dependent with a lowering of glycaemic index of the available carbohydrate. This is significant over all studies and in each food intake control category (**Fig 8** and **Table 6**).
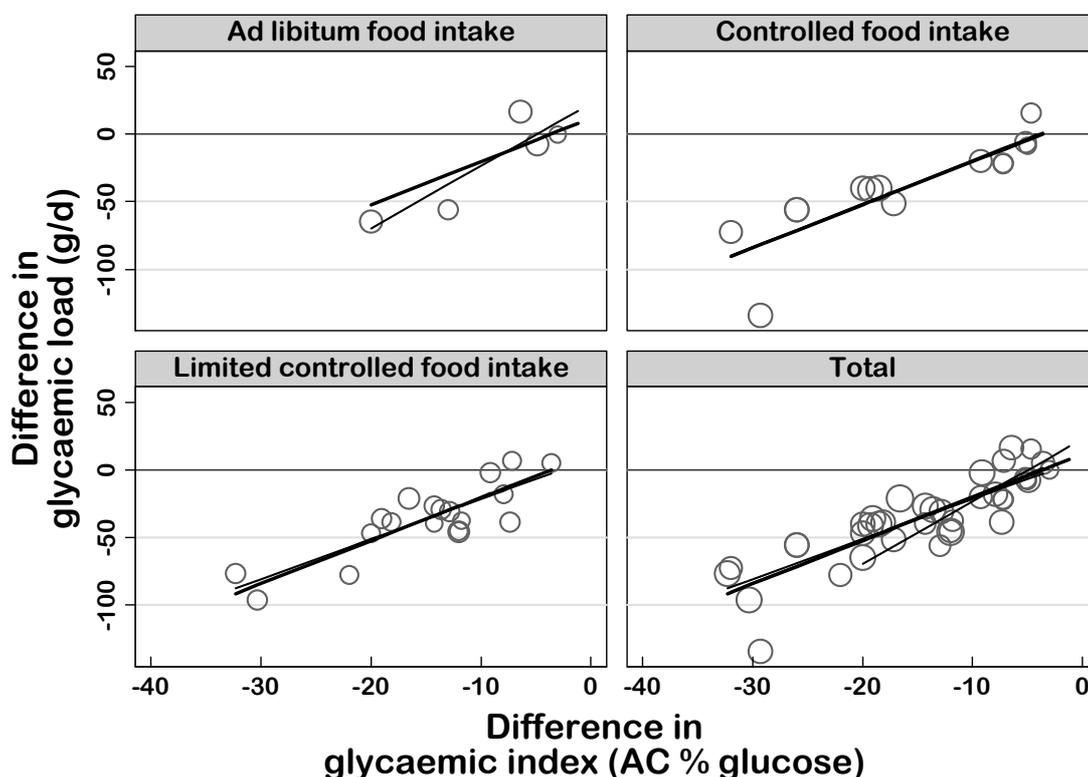
Fig 8: Difference in glycaemic load associated with difference in glycaemic index achieved. (See **Annex 20** for details on statistics and sources/references)

As a univariate determinant of glycaemic load, then glycaemic index of total carbohydrate is more predictive than is glycaemic index of available carbohydrate. The former gives an approximately two-fold improvement in the precision (or reduction in the 95% confidence interval as can be seen in **Fig 9** in **Annex 20(1)**). There is also a stronger slope, i.e. greater sensitivity (slope ratio for GI_T vs. GI_{AC} is 1.16; obtained as 3.6 divided by 3.1 for all studies combined (**Tables 6 & 7** in **Annex 20** and **21)**.

This is attributable to an exchange of approximately 1 g available carbohydrate with 1 g unavailable carbohydrate in all categories of food intake combined (1.09 g/g; significantly **Fig 10** and **Table 8** in **Annex 22(1)**) and consistently though not significantly in each of the three food intake control categories separately (1.00 to 1.31 g/g) (see **Fig 11** and **Table 8** in **Annex 22)**.

The approximate 1:1 exchange of available and unavailable carbohydrate suggests that in these intervention studies the outcomes overall may result from such an exchange in addition to the reported exchange of low for high glycaemic available carbohydrate.
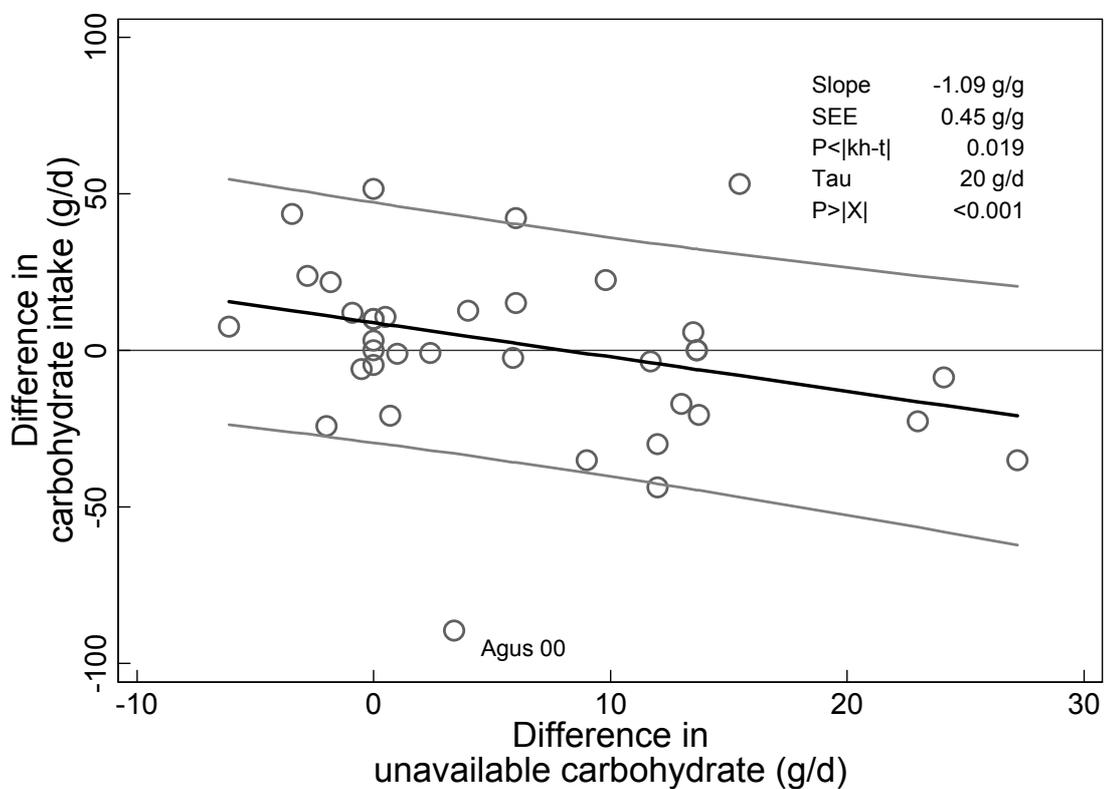
Fig 10:. Difference in available carbohydrate associated with difference in unavailable carbohydrate intake found. Each study is represented by a bubble proportional to the inverse of (Tau^2+SE^2). Curves are the regression line and the 95% confidence interval for the population of studies.

Macronutrients in relation to Glycaemic Load

The differences in the intake of metabolisable energy are more closely related to differences in glycaemic load (**Fig 12**) than to differences in glycaemic index of available carbohydrate (**Fig 3**).

Fig 12: Difference in metabolisable energy intakes associated with difference in glycaemic load found. Observations are grouped by the category of control over food intake (where total is all categories combined). Each study is represented by a bubble proportional to inverse (Tau^2+SE^2). To facilitate comparison the curves in each graph show the same bold random effects regression curve for all categories combined as well as the category random effects regression curves.

An initial jump upward and subsequent falling trend in metabolisable energy intake occurs in the ad libitum and limited (partial) control categories, but not in the control category (**Fig 12** and **Table 9** in **Annex 23**).

The differences in protein intake in relation to the differences in glycaemic load show less marked jumps and falling trends than for differences in metabolisable energy. These are significant over all studies combined, but not evident in the category of tight food control (**Fig 13** and **Table 10** in **Annex 24(1)**).

No difference in fat intake relative to the difference in glycaemic load is found, except for a possible falling trend with fall in glycaemic load in the ad libitum category (**Fig 14** and **Table 11** in **Annex 25**).

A rise in unavailable carbohydrate intake occurs with a lowering of the glycaemic load in these studies (**Fig 15** in **Annex 26(1)**). Whilst this is consistent among the food intake control categories, it does not reach statistical significance and is at a low rate (less that 7 g unavailable carbohydrate per 100 g eq.GL) (0.07g/g eq. glu in **Table 12** in **Annex 26(2)**).

A lower glycaemic load is in part accompanied (likely partly explained) by a markedly upwards jump in available carbohydrate intake followed by a substantial falling trend in carbohydrate intake in all food intake categories significantly, although this is less marked in the controlled food intake category it is still observed (**Fig 16** and **Table 13** in **Annex 27**).
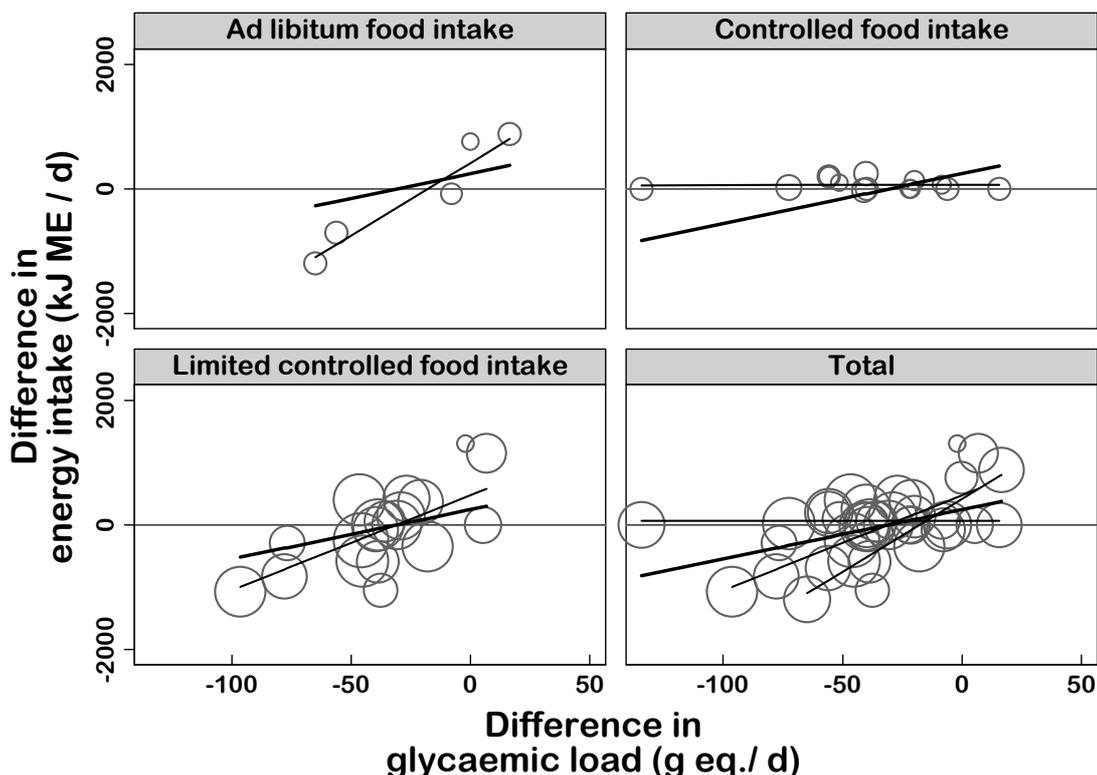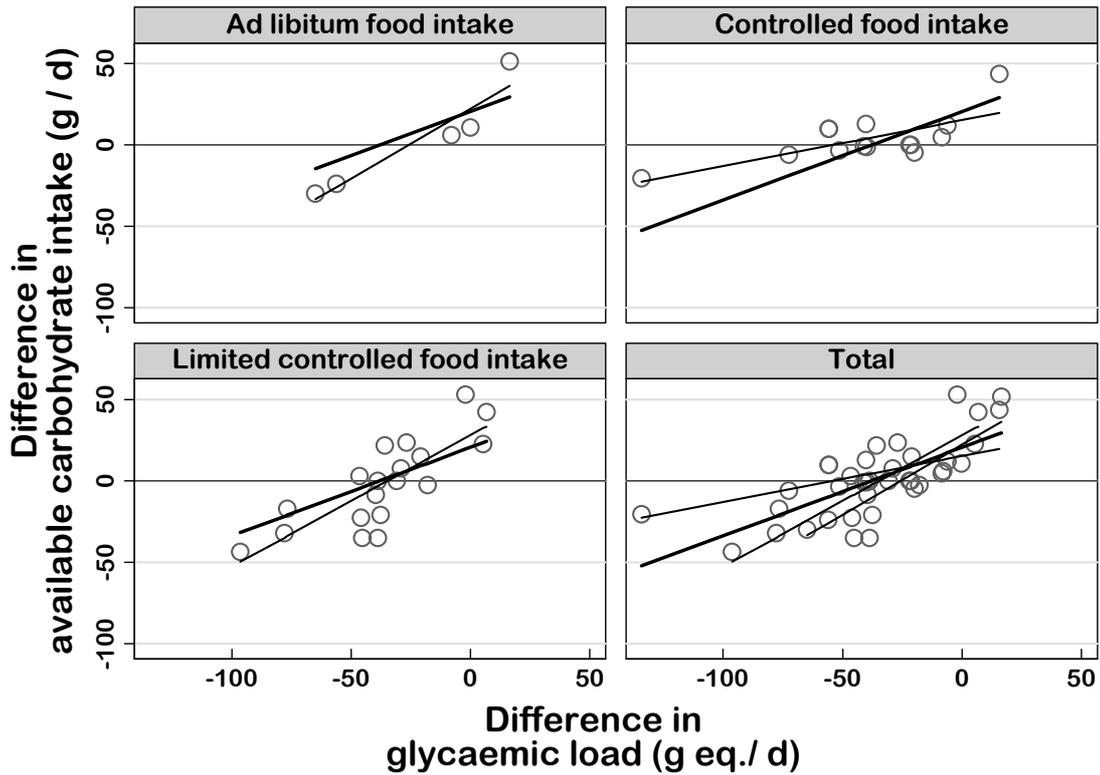
FIG 16: Difference in available carbohydrate intake associated with difference in glycaemic load found. Observations are grouped by the category of control over food intake (where total is all categories combined). Each study is represented by a bubble proportional to inverse (Tau^2+SE^2). To facilitate comparison the curves in each graph show the same bold random effects regression curve for all categories combined as well as the category random effects regression curves.

Metabolisable energy intake related to glycaemic aspects

After combining information from the ad libitum and limited controlled food intake categories and application of forwards and backwards stepwise REML random effects regression, it is clear that differences in metabolisable energy intake are most closely related to differences in available carbohydrate intake rather than to differences in either glycaemic index or glycaemic load (which mathematically is an interaction between carbohydrate intake and glycaemic index). **Table 14** shows the start and finish of the 'backward steps' to simplify

the 'explanatory model' beginning with all the glycaemic parameters and ending with available carbohydrate as most explanatory. The association with available carbohydrate is evident in each food intake control category, except where there is tight control **(Fig. 17** and **Table 15** in **Annex 28**). Remaining among study variance is 'explained' by variation in fat intakes (See **Annex 29** for details on fat intake related to combined glycaemic aspects).

TABLE 14 Difference in metabolisable energy intakes in intervention studies related to difference in the glycaemic aspects achieved in all studies excluding controlled food intake [1,2].

	k (df)	Available carbohydrate	Glycaemic index$_{ac}$	Glycaemic Load	Constant	I^2 (J^2/J^2) [3]	Tau (kJ/d) [4]
First step:							
Slope (kJ/ g)	24 (20)	20.1	0	1	5	0.42	179
SEE		8.9	33	14	155		
P>|kh-t|		0.036	0.994	0.951	0.98		
Intermediate step:							
Slope (kJ/ g)	24 (22)	21	-	-	-19	0.37	155
SEE		4	-	-	57		
P>|kh-t|		0.001	-	-	0.73		
Last step:							
Slope (kJ/ g)	24 (23)	21	-	-	-	0.36	145
SEE		2	-	-	-		
P>|kh-t|		0.001	-	-	-		

Sources:

Included studies: Those with information or calculable information on fat, available carbohydrate, GI and GL of treatment diets and provided ad-libitum or with only limited control of food intake: Bouche et al 2002, Brynes et al 2003 (Su), Brynes et al 2003 (St), Collier et al 1988 (d2), Ebbeling et al 2003 (d2), Fontvieille et al 1988, Frost et al 1994, Frost et al 1996, Frost et al 1998 (exp1), Frost et al 1998 (exp2), Frost et al 2004, Giacco et al 2000, Herrmann et al 2001 (expt2), Jenkins et al 1987b (all), Jenkins et al 1988, Jimenez-Cruz et al 2003, Jimenez-Cruz et al 2004, Komindr et al 2001, Lafrance et al 1998, Luscombe et al 1999, Rizkalla et al 2004, Sloth et al 2004 (d5), Tsihlias et al 2000 (d2), and Wolever & Mehling 2002a (d4).

Excluded studies: Those with tight control of food intake: Brand et al 1991, Calle-Pascual 1988 (exp1_T2), Calle-Pascual 1988 (exp2_T2), Carels et al 2005, Fontvieille et al 1992 ('exp1'), Fontvieille et al 1992 ('exp2'), Heilbronn 2002 (d2), Jarvi et al 1999, Jenkins et al 1987a (d2), Kiens et al 1996 (d4), Kurup 1992 (raggi vs rice), Kurup 1992 (raggi vs tapioca), Wolever et al 1992a (d3), and Wolever et al 1992b (d2).

Summary of relationships for GI, GL and Macronutrients:

i. Reductions in glycaemic index of intervention diets are commonly accompanied by reductions in glycaemic load greater than can be accounted for by the change in glycaemic index and fixed available carbohydrate intake.

ii. 'Dose' dependent reduction in glycaemic index is accompanied by an initial jump in carbohydrate intake followed by a trend falling towards much lower carbohydrate intakes, so explaining the wider range of glycaemic load than expected from the change in GI alone.

iii. The reduction in available carbohydrate intake contributes to a dose dependent reduction in metabolisable energy intake (and a greater reduction in net metabolisable energy intake due to a higher proportion of unavailable carbohydrate and protein in the diet).

iv. Glycaemic index of total carbohydrate predicts glycaemic load with precision approximately twice that for the glycaemic index of available carbohydrate. This is attributable to a g/g exchange of available and unavailable carbohydrate.

v. An absence of tight control on food intake when aiming for low glycaemic carbohydrate diets is not accompanied by an inverse relation between fat intake and either carbohydrate intake or glycaemic load, i.e. a rise in fat intake does not occur to compensate for the lower carbohydrate intake.

vi. There is some evidence of potential harm from inadequate attempts to lower glycaemic index due to a rise in glycaemic load as available carbohydrate intake may rise initially before falling at glycaemic loads reductions more than 50 g eq. glucose.

These findings derive from random effects meta-analysis and inverse variance REML random effects meta-regression analysis across studies. They apply to combined health and body weight types (healthy, IGT, hyperlipidaemia, T1DM, T2DM, primary and secondary CHD risk, and normal, overweight and

obese weight for height). Generally there is too little information for establishing the findings also in each of either health or body weight (BMI) type separately or significantly for interventions greater than 12 weeks duration. However, observations of a rise in carbohydrate intake with inadequate attempts at glycaemic index reduction, and so failure to reduce the glycaemic load, occurs in all three intake control categories (ad libitum, limited controlled and controlled food intake), implying that this may be difficult to escape without a change in approach to dietary modification. The bitonic effect accompanying attempts at GI reduction could explain confusion arising from individual studies reporting differing outcomes. The different outcomes for carbohydrate and energy intake appear to be real and not simply due to experimental error. More direct attempts to reduce the GL of diets (without elevating saturated fat intake) may avoid the inadequacy mention for glycaemic index.

Body weights

Preamble

Prior to 2005 there were 23 relevant studies reporting on body weight and change of glycaemic index from high to low glycaemic carbohydrate (variable high unavailable carbohydrate) diets. Of these 19 reported GI values (or information on foods to estimate GI). Among these studies, observations were from healthy (k = 4) or glucose intolerant (k = 1) or type-1 (k = 1) and type-2 (k = 9) diabetics or subjects at risk of primary or secondary coronary heart disease (k = 4). Two of the studies in healthy subjects were reported as 'in press' and another in subjects with impaired glucose tolerance had 3 repeats. Finally one study reported information analysed according to both a parallel design and a crossover design from which the crossover information was selected.
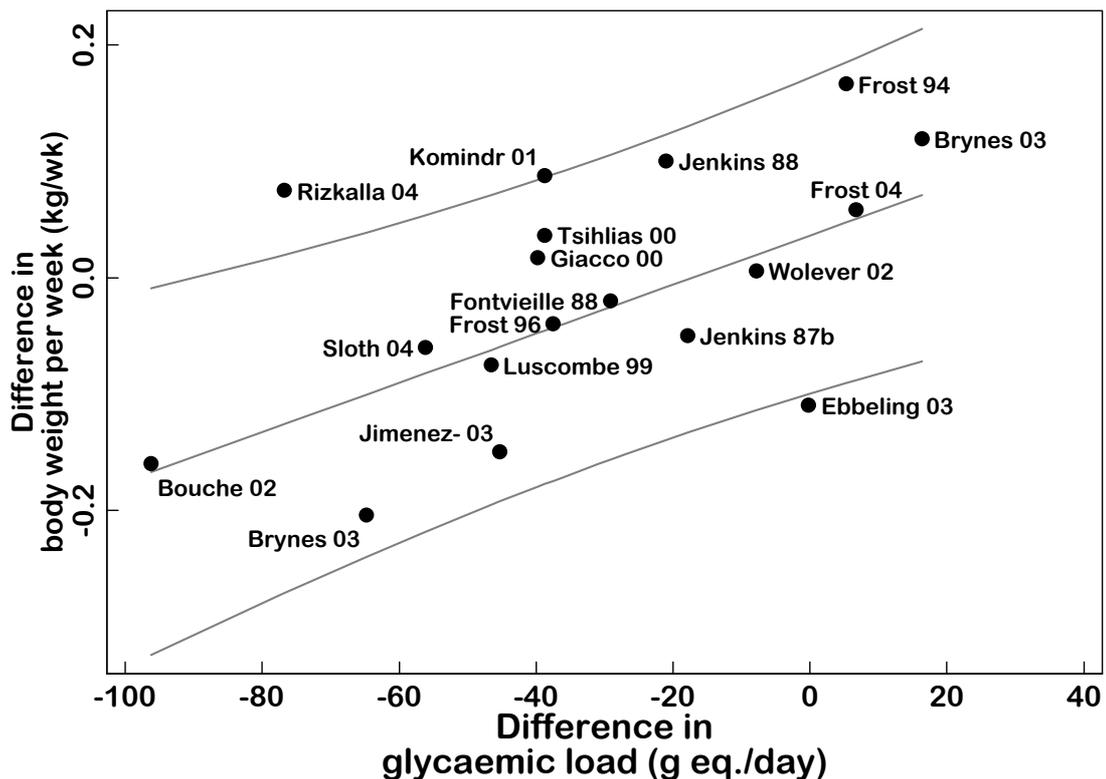
Fig 18: Evidence base relating difference in body weight to difference in the glycaemic load. The curves show the inverse error random effects REML meta-regression slope and 95% confidence intervals. Data are for ad-libitum and limited controlled food intake categories combined (k = 18) and are identified by the publication's first author and abbreviated year of publication, note that Jimenez 04, fell close by Jiminez 03). (See **Annex 30** for excluded studies)

Dietary methods difference

Combining information from all studies provided little understanding of the effect of treatment with low glycaemic index diets on body weight. Therefore other aspects of dietary composition, food intake category, and weight change were considered.

After elimination of studies with control over food intake (i.e. combining only ad-libitum and limited controlled food intake studies), the average weekly rate of change in body weight among studies is related to glycaemic load, and the relationship is statistically significant (P>|kh-t| =0.01) (**Table 17**). **Fig 18** identifies the co-ordinates of included studies. Studies excluded by reason are given in **Annex 30**.

Such a relationship between difference in body weight and difference in glycaemic load is evident somewhat also in the ad-libitum food intake category alone, and again in the limited controlled food intake category alone, though each category alone does not reach statistical significance (**Fig 19** and **Table 18** in **Annex 31**). The relationship remains statistically significant over all studies combined, though a dilution effect is then evident due to studies from the control food intake category, which have no effect.

TABLE 17: The influence of dietary characteristic (inclusion/exclusion) on the parameter estimates relating the difference in **body weight** to the treatment difference in the glycaemic and unavailable carbohydrate character of diets. [1]

Dietary component or character (units)	k (df)	Slope (g wk^{-1} per unit)	SEE	P>|kh-t|	Tau (kg/wk)	I^2 (kg/wk)^2
Glycaemic load (g. eq/d)	19 (17)	2.1	0.7	0.01	0.071	0.75
Glycaemic index$_{AC}$ (% glucose)	19 (17)	6.9	3.2	0.05	0.080	0.83
Glycaemic index$_{TC}$ (% glucose)	18 (16)	6.6	3.3	0.06	0.082	0.83
Metabolisable energy (kJ/d)	20 (18)	0.08	0.04	0.05	0.097	0.84
Fat (g/d)	20 (18)	4.0	4.0	0.36	0.109	0.86
Available carbohydrate (g/d)	20 (18)	2.4	1.0	0.04	0.097	0.88
Protein (g/d)	19 (17)	4.0	4.0	0.33	0.110	0.91
Unavailable carbohydrate (g/d)	18 (16)	0.7	3.5	0.85	0.102	0.92

Abbreviations: k, number of studies; df degrees of freedom; SEE, standard error of estimation;
[1] P>\|kh-t\|, level of significance based on Knapp-Hartung-t; Tau, among studies error; I^2, proportion of variance due to among study variance.

Among different possible determinants of the body weight change in response to treatment (**Table 17**), univariate inverse variance random effects meta-regression indicates glycaemic load to be the most significant; more than either available carbohydrate intake or glycaemic index or metabolisable energy.

Progressive body weight reduction (or relative lack of weight gain) is evident among studies with a glycaemic load reduction >50 g eq. per day from either the ad libitum food intake or limited controlled intake categories (**Fig 20**). Studies with the largest body weight response were for 12 or more weeks duration in young adults or children who were overweight or obese though otherwise healthy (**Table 19**).

TABLE 19:. Body weight responses to low glycaemic carbohydrate diets.

Health	Weight class	Age (y)	Body wt response (kg)		Study ID
			mean	SEE	
Less than 12 weeks:					
CHD risk	Overweight	45	-0.7	0.1	Brynes et al 2003 (st)
Type-2 DM	Obese	57	-0.3	0.8	Luscombe et al 1999
Type-2 DM	Obese	54	0.3	0.7	Rizkalla et al 2004
Healthy	Overweight	46	-0.8	0.3	Bouche et al 2002
Type-2 DM	Overweight	59	-0.9	1.9	Jimenez-Cruz et al 2003
Healthy	Overweight	30	-0.6	0.7	Sloth et al 2004 (d5)
12 or more weeks:					
Healthy	Overweight	-	-1.8	0.8	Price (in press 2005)
IGT	Overweight	35	-2.43	0.4	Slabber et al 1994 (exp2)C
Healthy	Obese	10	-3.34	0.5	Spieth et al 2000
Healthy	Obese	16	-5.7	2	Ebbeling et al 2003
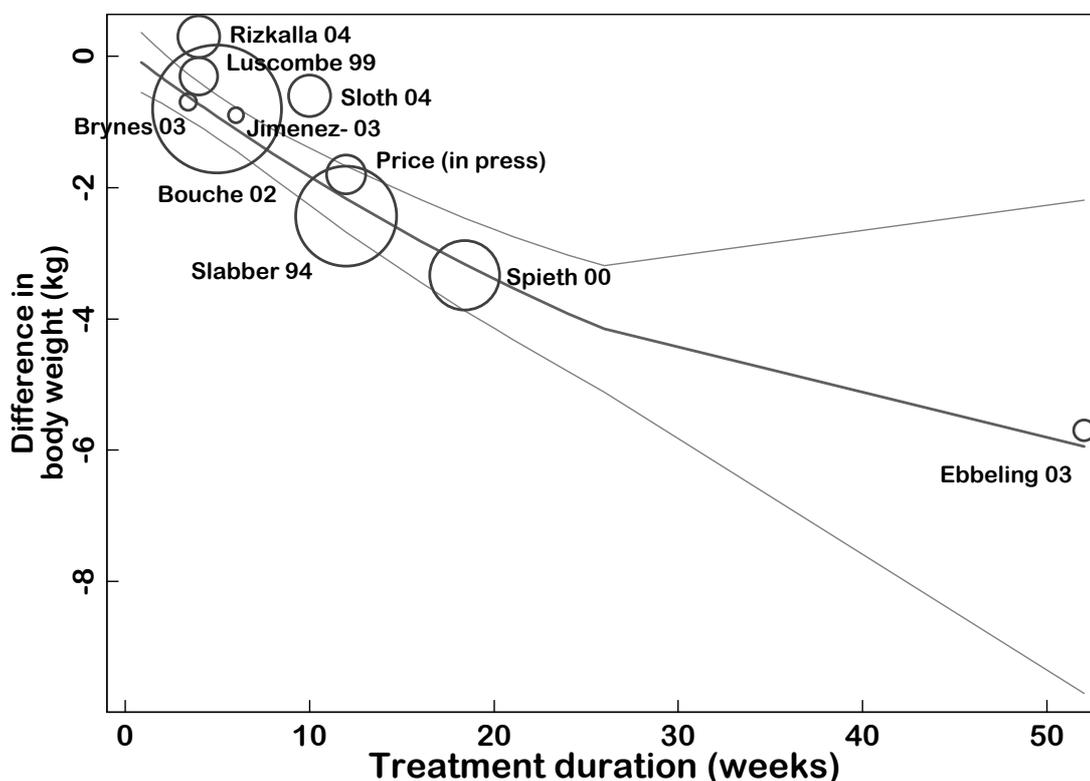
FIG 20: Evidence base relating difference in body weight (control – low GI treatment at the end of study) to duration of low-glycaemic treatment. The curves show the inverse-error random effects REML meta-regression curve and the study population 95% confidence intervals. Possibility of curvature in the plot was permitted using duration and square of duration as determinants. Bubbles show the relative precision of each study, i.e. the inverse (Tau^2+SE^2) (k = 10, df = 7) and are identified by the publication's first author and abbreviated year of publication. See **Annex 32** for included and excluded studies.

Summary GI, GL and Body Weight:

i. Change in body weight due to treatments among intervention studies significantly associates with the change in the diets glycaemic load.

ii. In univariate analysis, glycaemic load appears to be as good or better than other factors (metabolisable energy intake, glycaemic index, available or unavailable carbohydrate intake) as a determinant of the body weight response.

iii. Studies designed to address the question of body weight response to low glycaemic carbohydrate diets together with those in which a reduction in glycaemic load of 50 or more g. eq. per day is achieved without tight control of food intake, show a combined body weight response significantly dependent upon the duration of study.

iv. Over all studies, body weight reductions have not been achieved with confidence by more than 2 kg (upper 95% CI). Equally, body weight reductions as great as 8 kg appear possible (lower 95% CI).

Fasting glucose

Preamble

By Jan 2005, thirty-six relevant studies were reported on fasting glucose in either venous plasma or capillary blood. For analysis fasting venous plasma glucose was converted to the capillary blood glucose equivalent. Among these studies observations were from either normal healthy (k = 8) or glucose intolerant (k = 2) or type-1 diabetics (k = 5*) or type-2 diabetics (k = 17*) or subjects at risk of primary (k = 4) or secondary coronary heart disease (k = 1). * One study was reported in the literature with observations combined from type-1 and type-2 diabetics.

Dietary methods difference

A dietary methods difference plot showed the treatment differences to be most common when the average fasting blood glucose concentration was high (**Fig 21**). The figure shows data from all 36 studies and includes 14 intermediate observations (repeats) so totalling 50 observations. Reductions in the glycaemic index of diets ranged from 4 to 32 (Glucose=100) and were for periods from 2 to 26 weeks. The accompanying reductions in glycaemic load ranged from 6 to 134 g glucose eq. These changes were sometimes accompanied by targeted (or accepted) or untargeted elevations in unavailable carbohydrate intake.
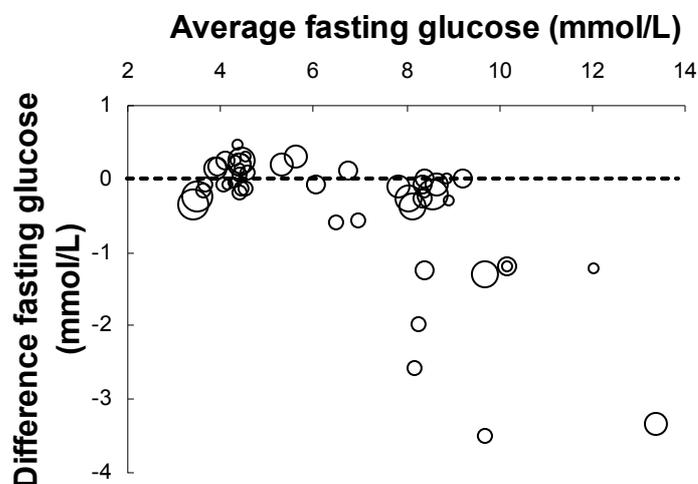
FIG 21: Dietary methods difference plot of the response of fasting blood glucose to variably lower glycaemic (variably higher unavailable carbohydrate) treatment.

Bubbles show the relative size of studies ($\sqrt{n}$) for 32 studies and 14 repeated (totalling 50 bubbles) available prior to 2005.

Fasting glucose <5mmol/L

Random effects meta-analysis shows no overall reduction in fasting blood glucose when the study population mean is ≤ 5mmol/l as shown (**Fig 22**) for the healthy subjects (8 studies), subjects with impaired glucose tolerance (2 studies) and subjects at risk of primary CHD (4 studies) combined. Rather the fasting blood glucose was elevated (from below 5mmol/L) to a small though significant extent over all studies for this group with "moderate hypoglycaemia" (> 3 mmol/L to <5 mmol/L capillary glucose).
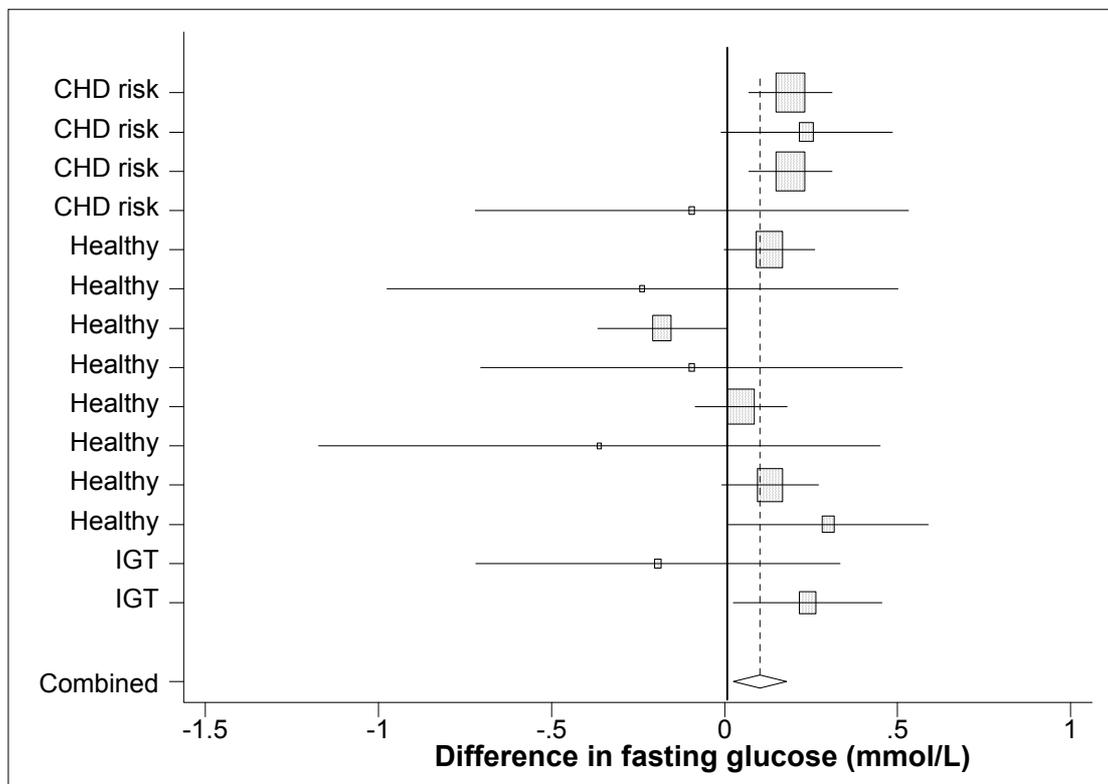
Fig 22: Fasting Glucose <5mmol/L (legend: see figure next page):

Impact of lower glycaemic (variably higher unavailable carbohydrate) diets for 1 to 16 weeks on the fasting blood glucose in groups of people without diabetes and with fasting glucose ≤5 mmol/L. The combined random effects estimate is +0.1 (0.03 to 0.2), P>|z| = 0.009, and k = 14 studies. Point estimates are mean and sed for each study, and the relative point size indicates the relative study weight.

Fasting glucose>5mmol/L

At higher concentrations, there was good evidence of a reduction in fasting blood glucose concentration with increase in the severity of the abnormality in this clinically defining parameter. Random effects meta-regression showed (**Table 20** in **Annex 33**) a highly significant relation to severity of this abnormality. The slope of the regression line has meaning in that it is the fractional correction (or prevention of deterioration) of the abnormality in fasting glucose, one diet relative to the other. The fractional correction was 0.3 (or 30%). The standard error of estimation and estimated level of significance of this fraction depended to some extent on the method of random effects regression (method or moments, residual maximum likelihood) and test of significance (z-score, Knapper-Hartung t, Monte Carlo permutation), though in no case was the conclusion different. Among the 22 studies (without intermediate duration data), four investigated sub-maintenance diets; eliminating these from the analysis, such that all the remaining 18 studies investigated diets were intended to be at maintenance, yielded the same result (**Table 20** in **Annex 33**).

Control for macronutrients

Among studies there is some variation between treatments in energy, carbohydrate, fat, protein and unavailable carbohydrate intake. However, the fractional correction to 'capillary' glucose was mostly insensitive to tightening of macronutrient control achieved by progressively excluding those studies with the largest between-treatment differences in these dietary parameters, according to the limits specified at the foot of **Table 21** in **Annex 34**. To avoid substantial loss in power by dropping studies, the treatment differences in dietary components were implemented as possible covariates (**Table 22** in **Annex 35**). This approach enabled also an examination of the impact of glycaemic load and glycaemic index as possible independent determinants. Again, dependence of the effect size on the severity of abnormal fasting glucose remained at a fractional correction of about 0.30 (or 30%). None of the potential covariates (energy, protein, fat, available carbohydrate, unavailable carbohydrates, GL, GI) were sufficiently determinant by

<u>themselves</u> or collinear with severity to confound the analysis; none displaced fasting glucose as a determinant of the effect size.

Interaction with severity

Given severity of the abnormality in fasting glucose as a factor that determines the effect size on treatment with low versus high glycaemic carbohydrate diets (as evident above), the macronutrient intake might be expected to interact with severity to affect the treatment outcome. No single dietary factor was identified that interacts with severity to explain the effect size more precisely than severity alone; this was evident for energy, fat, protein, available carbohydrate and sugars. To the extent that such changes occurred in these factors, randomness was introduced that elevated the estimate of among-study variance (Tau^2, **Table 23** in **Annex 36**). Glycaemic index and glycation index (see **Table 24** in **Annex 37**) each removed some randomness as they decreased the estimate of among-study variance, while glycaemic load tended to increase it (Tau^2, **Table 24** in **Annex 37**). While no single dietary component was found to interact with severity to explain variation in results between studies, a possibility remained that other factors or combinations of examined factors or both would explain the remaining among-study variance.

Role of both glycaemic and unavailable characteristics

There is good evidence that change in both the glycaemic character of the 'carbohydrate' and change in the unavailable carbohydrate content of diets will each independently interacted with severity of abnormality in fasting glucose to improve the outcome. This find from the intervention studies occurs with a number of different modes of expression of these two characteristics of the diet (**Table 25** in **Annex 38**), and leads to deceases in the remaining estimate of the among-studies variance, Tau^2. However, comparison of Tau^2 by F-ratios indicates that although glycaemic load can be used instead of

glycaemic index no one mode of expression of the glycaemic characteristic was a significant improvement over any other.

Evidence of such roles for the unavailable carbohydrate and the glycaemic character of the diet is independent of possible choice of studies. Thus all studies combined (31 studies) or studies after excluding some types while still retaining a range of fasting glucose (14 studies remaining) yielded similar outcomes (**Table 26** in **Annex 39**) and did not affect the finding that the unavailable carbohydrate content of the diet in studies on 'glycaemic index' was a significant determinant of the fasting glucose. The study exclusions were progressively: fasting glucose <5mmol/l, sub-maintenance food intakes, then a study with a potentially outlying residual. No exclusion yielded an influence statistic for $\Delta\hat{\beta}_{ij}$ >1 for either the glycaemic parameter or unavailable carbohydrate. Thus the overall result appears reliable and unexplained by aggregation of observations from these different types of studies.

Plausibility of individual study outcomes in respect of unavailable carbohydrate and glycaemic response

Individual intervention study results expressed according to glycaemic index (per AC) and unavailable carbohydrate show plausible outcomes (**Fig 23**). Visual inspection shows no study to be markedly discrepant from the overall result. Observations on effect size for fasting glucose versus the unavailable and glycaemic character of carbohydrate was observable also when the later characteristic was expressed in other forms, for example: replacing glycaemic index of available carbohydrate with glycaemic index of total carbohydrate (**Fig 24** in **Annex 40**). A similar observation was made when using *aglycaemic* carbohydrate (available carbohydrate less glycaemic load) to express the glycaemic characteristic of the diet (**Fig 25** in **Annex 41**).
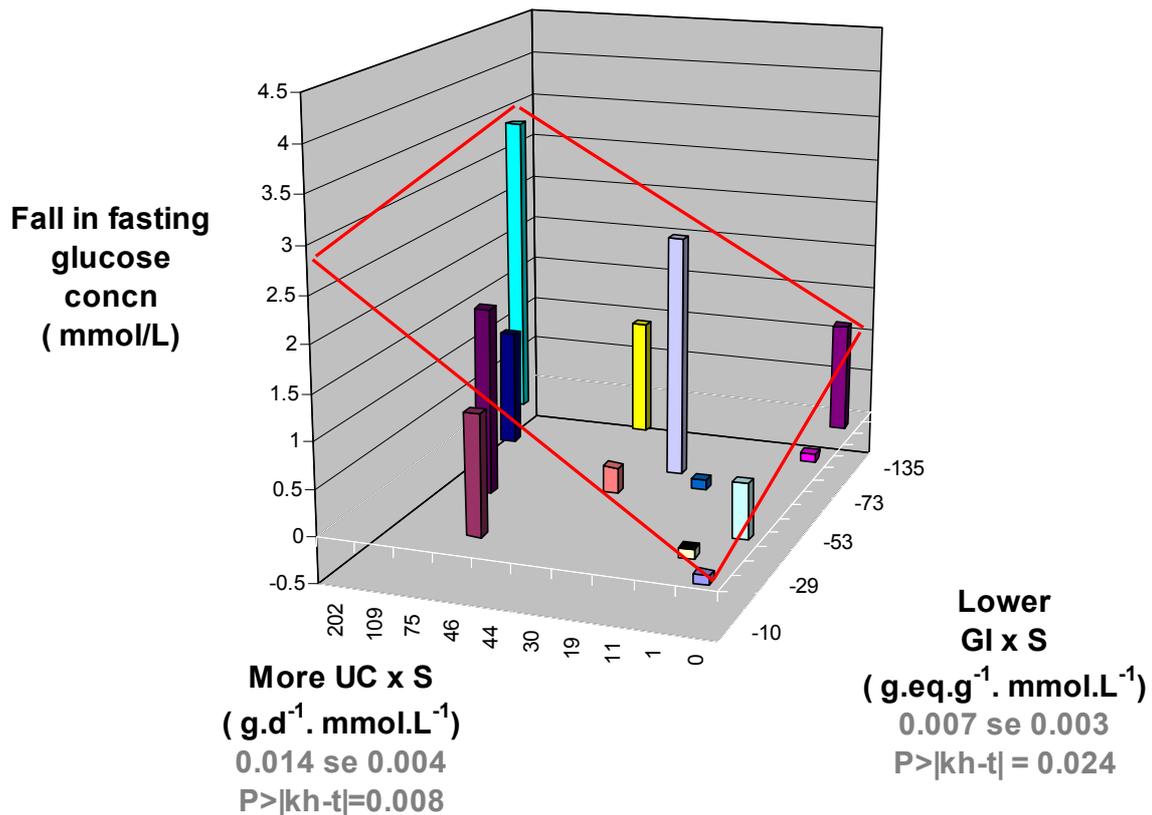
Fig 23: A tri-variate set of determinants of the effect size for reduction in fasting glycaemia. Severity of abnormality in fasting glucose (S = FBG – 5 mmol/L), unavailable carbohydrate (UC) and glycaemic index (GI_{AC}) are the explanatory variables. NB axes rise discontinuously. Each vertical bar is an individual study. The tilted quadrangle joins predicted points at each corner with straight lines.

The last figure (**Fig 25** in **Annex 41**) includes all 31 studies, and so has a wider range of observations because this includes fasting blood glucose < 5mmol/L as well as >5 mmol/L. The figure also shows quadrangles derived with and without a potentially outlying study. Views of **Fig 25** right-hand side (**Fig 26** in **Annex 42**) and from the front side (**Fig 27** in **Annex 42**) show more clearly the importance of unavailable carbohydrate and aglycaemic carbohydrate respectively, and that the outlying information is more outlying for unavailable carbohydrate than for aglycamic carbohydrate. In regard this outlying study, the study effect size was not significantly different from zero and was 4.2 jack-knifed residual standard deviations from the expected result based on all studies combined. Hence the study might be considered a statistical outlier. Notably, however, the influence on the overall outcome was

very small relative to that of all other studies combined (influence statistic $\Delta\hat{\beta}_{ij}$ of 0.18, and Cooks D of 0.15, each less than the critical value of 1). Hence the outlier had virtually no influence on the overall result.

Normalisation of fasting glycaemia

There is some evidence of a small but significant rise in fasting glycaemia among 14 studies with fasting glucose below 5 mmol/L (**Fig 22**).

Among studies with information on the unavailable and aglycamic carbohydrate, a rise in fasting glycaemia is apparent in **Fig 25** in **Annex 41** where it is represented as a negative fall in fasting glucose (white columns) and includes 7 such studies. Two other studies for which similar dietary information is available also showed an absolute elevation in fasting glucose (statistically significant or not) and had fasting blood glucose <7 mmol/L.

The relationship between change in fasting glycaemia and change in aglycaemic carbohydrate intake was similar above and below a fasting glucose concentration of 5 mmol/L (**Table 27**), though did not reach statistical significance below 5 mmol/L. A similar observation was made for the change in unavailable carbohydrate (**Table 27**).

Relative importance of unavailable and aglycaemic characteristics

In each two way random effects meta-regressions performed the sensitivity of fasting glucose to dietary change was greater for the unavailable carbohydrate than for the aglycaemic carbohydrate or glycaemic load (**Table 26,** and **Tables 27** in **Annex 42**). This can be seen also in **Figs 23, 24** and **25** for glycaemic index, whether based on glycaemic index per unit available carbohydrate or per unit total carbohydrate. The statistical significance of this difference in sensitivity between unavailable and aglycaemic carbohydrate was P>|kh-t|<0.05 when all studies were combined (n=31).

TABLE 27: The influence of study characteristic (inclusion/exclusion) on the parameter estimates relating the difference in fasting glucose to difference in the glycaemic and unavailable carbohydrate character of diets

k (df)	Glycaemic character			Unavailable character			Tau^2	I^2
	Coefficient	SEE	P>|kh-t|	Coefficient	SEE	P>|kh-t|		
	S x Δ(AC-GL)[1]			S x Δ UC[1]				
All studies								
31(29)	-0.0030	0.0009	0.00	-0.011	0.003	0.00	0.01	0.54
Studies with fasting glucose > 5 mmol/L								
19(17)	-0.0032	0.0012	0.01	-0.011	0.004	0.02	0.02	0.58
Studies with fasting glucose <5 mmol/L								
12(10)	-0.0033	0.0017	0.07	-0.008	0.009	0.42	0.01	0.54

Abbreviations: k, number of studies; SEE, standard error of estimation; P, level of significance based on Knapp-Hartung-t, Tau^2, between study variance; I^2, proportion of variance due to between study variance; S, severity of abnormality in fasting glycaemia; GL, glycaemic load, AC, available carbohydrate.
1. Units: mmol.L-[1] per g change in aglycaemic carbohydrate or unavailable carbohydrate

Consequence of using total carbohydrate in place of available carbohydrate

In countries or regions where measures of unavailable carbohydrate are not readily to hand, which included the USA and many regions of interest to FAO, the calculation of aglycaemic carbohydrate using total carbohydrate rather than available carbohydrate results in exactly the same effect size estimate for influence on blood glucose of the aglycaemic carbohydrate (**Fig 28** in **Annex 43**). Doing so however reduced the effect size related to the unavailable carbohydrate (**Fig 28**).

Applicability to all groups of people.

There is good evidence that effects in all groups of individuals examined here are predictable according to severity of fasting glucose, the change in the intakes of unavailable carbohydrate and the change in the intake of *aglycaemic* carbohydrate (**Table 27**, n=31; **Fig 29**). Thus the observed treatment difference in fasting glucose for different health types is insignificantly different from those predicted **Fig 29**. However, reductions in fasting glycaemia were seen only in the diabetic groups with greatest reductions in type-1 diabetics, though only in line with a greater abnormality in fasting glucose.
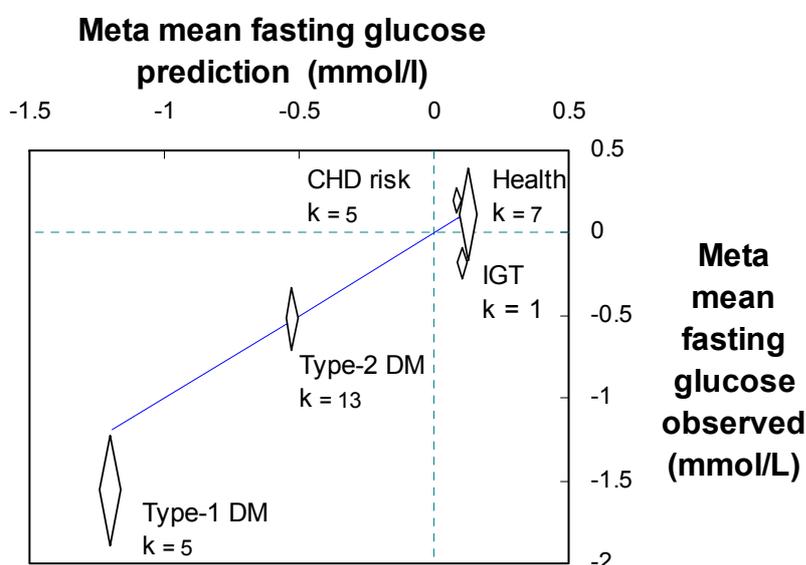
Fig 29: Treatment difference in fasting glucose in patients and healthy people: deviation of observed from predicted values by health group. A random effects meta-analysis is shown of residual deviations from predicted values based on the model ΔFBG = -0.03 S.ΔUC -0.011 S.Δ(AC-GL) (Table 8, k = 31 studies) where S is severity of abnormality in fasting blood glucose (FBG-5),   UC is   unavailable carbohydrate intake and AC-GL is aglycaemic carbohydrate intake. Diamonds show the combined or meta mean (mid point of diamond) and residual standard error for the health type (vertical distance from mid-point to vertical points). Der Simonian and Laird estimates of between studies variance were 0.34 (Q= 7.4; P=0.115) for deviations among type-1 diabetics; 0.19 (Q=29.4, P=0.003) for type-2 diabetics, zero for patients at risk of 1° or 2° CHD (where random = fixed effect) and undeterminable in the glucose intolerant group (only one study with dietary data).

Applicability in diabetics

The influences of unavailable carbohydrate and aglycaemic carbohydrate appear to be similar across each diabetic group, though these influences are statistically significant only when diabetic groups are considered together (**Table 28**) or only for unavailable carbohydrate in the type-2 diabetics (**Table 28**). Thus there was insufficient evidence in type-2 diabetics alone to demonstrate a significant effect of the glycaemic character of the carbohydrate – this albeit that the magnitude of influence was numerically similar to that in all diabetics considered together.

TABLE 28: Random effects meta-regression estimates of the influence of unavailable carbohydrate and aglycaemic carbohydrate in diabetic groups (degrees of freedom = k-2).

k	Glycaemic character			Unavailable character			Tau^2	I^2
	Coefficient	SEE	P>|kh-t|	Coefficient	SEE	P>|kh-t|		
	S x Δ(AC-GL)[1]			S x Δ UC[1]				
All studies								
31	-0.0030	0.0009	0.00	-0.011	0.003	0.00	0.01	0.54
Type-1 & 2 diabetics alone combined								
18	-0.0033	0.0012	0.02	-0.011	0.004	0.02	0.02	0.59
Type-2 diabetics								
13	-0.0029	0.0015	0.09	-0.014	0.057	0.04	0.03	0.63
Type-1 diabetics								
4 [2]	-0.0034	0.0014	0.131	-0.009	0.005	0.22	0.00	0.241
5 [2]	-0.0044	0.0031	0.251	-0.006	0.009	0.52	0.86	0.631

Abbreviations: n, number of studies; SEE, standard error of estimation; P, level of significance based on Knapp-Hartung-t, Tau2, between study variance; I2, proportion of variance due to between study variance; S, severity of abnormality in fasting glycaemia; GL, glycaemic load, AC, available carbohydrate.

1. Units: mmol-L[1] per g change in aglycaemic carbohydrate or unavailable carbohydrate

2. The potentially outlying study was omitted from k=4 though included in k=5 (influence Δβij = 0.7 < Δβij critical = 1)

Replacement of aglycaemic carbohydrate with either glycaemic load or glycaemic index did not lead to greater statistical significance (**Table 29** in **Annex 44**).

While treatment with a low glycaemic carbohydrate diet resulted in a fall in fasting glycaemia in diabetics, a trend towards a small rise in fasting glycaemia was seen in the most influential studies on healthy groups of individuals (**Fig 30**). This rise was, on the whole, predictable from the model based on severity of abnormality in fasting glucose and the change in unavailable carbohydrate and aglycaemic carbohydrate intake (**Table 27**, n=31). There was too little data with too small effects to assess whether this predictable effect is attributable to the unavailable carbohydrate and aglycamic carbohydrate together in the proportions indicated in the model. Studies inside the 95% confidence interval were the most precise (larger bubbles) while those outside this interval were the least precise (smaller bubbles).
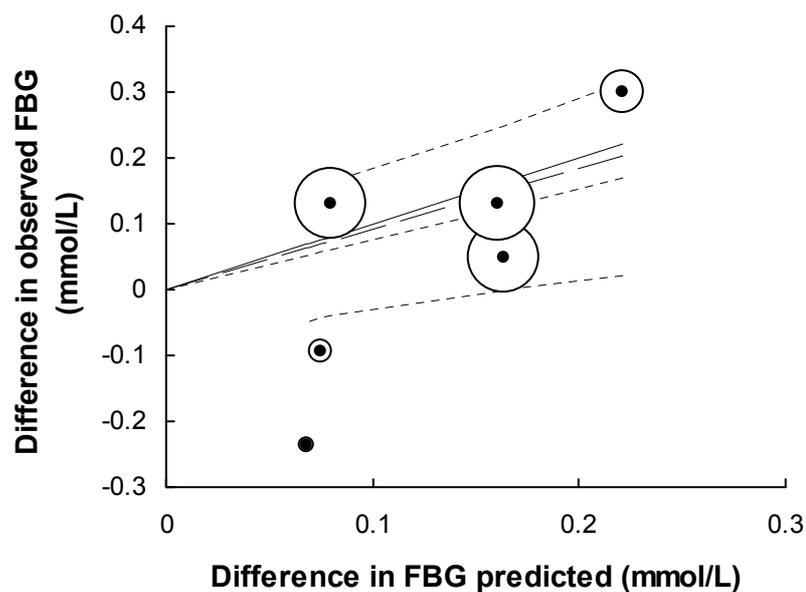
Fig 30: Trend for difference in fasting blood glucose (FGB) comparing model predicted differences with observed differences for studies with groups of healthy individuals. Predictions are based on the severity of abnormality in fasting glycaemia and changes in unavailable carbohydrate and aglycaemic carbohydrate ingestion during treatment (Table 8, k = 31 studies). Bubbles show study weights (inverse variance). The line of identity is shown (— —). For comparison, the model fit to diabetics is extrapolated here (— — —).The random effects regression line for studies of healthy participants (--------) and the corresponding 95% confidence intervals for the population of studies (--------). The meta-regression indicated a

slope of 0.76 SEE 0.26 (P> |kh-t| = 0.027) given the model is correct to pass through an origin with no effects when fasting glycaemia is 5 mmol/L.

Applicability to studies of 12 weeks duration or more

Studies of 12 weeks treatment duration or more should be performed to assess clinical relevance. Predicted outcomes matched the observed outcomes whether studies were of <12 or ≥12 weeks treatment duration (See **Table 30** in **Annex 45(1)** for more info on duration impact).

Summary GI, GL and Fasting Glucose:

i. There is strong evidence of a reversal in the abnormality in fasting blood glucose by consuming lower glycaemic higher unavailable carbohydrate diets.

ii. Within 12 weeks approximately 30% of the abnormality in fasting blood glucose can be rectified, and this percentage appears not to be explained by differences within studies in metabolisable energy, protein, fat or available carbohydrate intake between treatments, either independently or with interaction at higher blood glucose concentrations.

iii. A large contribution to the 30% effect is associated with a higher intake of unavailable carbohydrate. Indeed, bivariate inverse variance REML meta-regression indicates the correction appears more sensitive to unavailable carbohydrate than to glycaemic load (or any index of glycaemic load) on a weight for weight basis.

iv. Bias towards an effect of unavailable carbohydrate on fasting blood glucose cannot be entirely excluded – by chance studies with severely diabetic patients may well have emphasised diets with more unavailable carbohydrate when planning or advising the consumption of low-glycaemic carbohydrate diets. However, the outcome is consistent with epidemiological studies indicating both glycaemic load (or its index to carbohydrate) and unavailable

carbohydrate are each protective in respect of type-2 diabetes and coronary heart disease.

v. "Dose-dependent-like" effects of unavailable carbohydrate and glycaemic load (or its indices) were evident in all studies combined (healthy, glucose intolerant, type-1 & 2 diabetes, 1° and 2° CHD risk, hyperlipidaemics) only when expressed as interacting with the size of abnormality in fasting glucose (or departure from 5 mmol/L).

vi. At 5 mmol/L fasting blood glucose was not affected by low-glycaemic variably higher unavailable carbohydrate diets.

vii. At below 5 mmol/L fasting blood glucose, low glycaemic carbohydrate higher unavailable carbohydrate diets can increase the fasting blood glucose concentration to a small extent.

viii. Because there is good evidence that these diets cause fasting blood glucose to fall when above 5 mmol/L but rise when below 5 mmol/l, it appears that the diets have a normalising influence on blood glucose control operating in healthy people as well as in diabetics.

ix. Among few studies in patients at risk of primary or secondary (event) coronary heart disease, or with hyperlipidaemia or with impaired glucose tolerance, the fasting blood glucose values were too close to 5 mmol/L (according to predictive models) to expect significant change in fasting blood glucose due to the consumption of lower-glycaemic higher unavailable carbohydrate diets.

x. A predictive model general to all healthy people and patient groups included here, and that predicts changes in fasting glycaemia based on severity of abnormality in fasting glucose and diet composition (unavailable carbohydrate content and the glycaemic character), indicates outcomes for studies <12 and ≥12 weeks duration would be similar. There were few studies of the latter type, nevertheless they behaved as predicted.

xi. Should it be helpful in communicating the types of diets that appear effective in managing risk without attendant risk of elevating dietary fat intake, aglycaemic or total aglycaemic carbohydrate is a quantity effective in normalisation of fasting blood glucose.

Glycated proteins

Preamble

Prior to 2005, among the studies identified 28 reported on glycated protein concentrations. Measures include glycated albumin, glycated plasma protein, fructosamine and HbA_{1c}, which contribute 2.5, 2.5, 37 and 58% of the available data respectively). Participant groups were healthy (k = 2, one providing a repeated observation), primary CHD risk (k = 1), impaired glucose tolerance (k = 1 with three repeat observations), type-1 diabetes (k = 7, one with one repeat), type-2 diabetes (k = 16, one with three repeats and two with one repeat), and hyperlipdaemic patients (k = 1, mixed categories of hyperlipidaemia). When combined, these total 38 effect estimates.
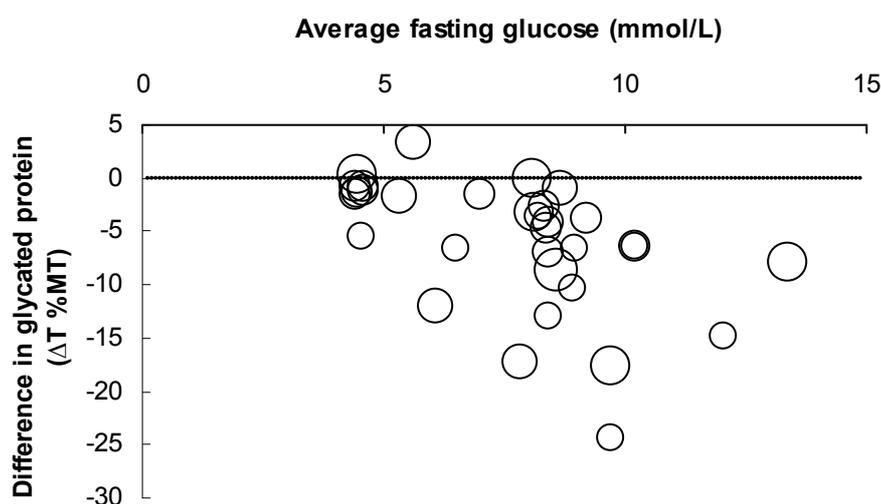
Fig 32: Dietary methods difference plot for all available data prior to 2005 on glycated protein concentrations; lower glycaemic variably higher unavailable carbohydrate treatment values less higher glycaemic carbohydrate low unavailable carbohydrate treatment. Bubbles show the relative size of the study ($\sqrt{n}$) for 28 studies and 10 repeats (totalling 38 bubbles). Participant groups were healthy (k = 2, 1 repeat, bubbles = 3), primary CHD risk (k = 1), impaired glucose tolerance (k = 1, one with three repeats, bubbles = 4), type-1 diabetes (k = 7, one with one repeat, bubbles = 8), type-2 diabetes (k = 16, one with three repeats, two with one repeat, bubbles = 21), and hyperlipidaemic patients (k = 1, mixed categories of hyperlipidaemia). Due to variation in measurement methods, the treatment average fasting blood glucose was used in place of average fasting glycated protein concentrations, and treatment difference is expresses as a percentage of the treatment average. Glycated proteins measures are for glycated albumin, glycated plasma protein, fructosamine and HbA_{1c}, which contribute 2.5, 2.5, 37 and 58% of the data respectively.

Methods difference

There is good evidence based on all 38 effect estimates of a fall in glycated protein concentrations on consumption of diets of low glycaemic higher unavailable carbohydrate content (**Fig 32**). The effect size is evidently dependent on the severity of abnormality in fasting blood glucose concentration.

Visual inspection of **Fig 32** would appear to suggest an intercept on the fasting blood glucose concentrations of about (or below) 5mmol/L. However, the random effects linear regression does not find a unique minima in Tau^2 at this concentration. Dropping intermediate observations (to avoid bias towards those studies with them) and forcing an intercept (from 0 to 8 mmol/L fasting glucose) yields increasing estimates of Tau^2 (**Fig 33** in **Annex 46**). The minima in Tau^2 is evidently below a fasting blood glucose value of 7 mmol/L (above which there is clinical concern) and indicates an intercept at ≤5 mmol/L (**Fig 22**).

The greater effect of low-glycaemic carbohydrate variably higher unavailable carbohydrate diets in people with higher fasting glucose concentrations is statistically significant using either all measures of glycated protein combined or fructosamine alone, thought is not statistically significant for HbA_{1c} alone, even though a similar trend is evident (**Table 31** in **Annex 47**). Since some studies are of short duration, adjustment to correct for the half-life of fructosamine (2.5 weeks) and HbA_{1c} (4.5 weeks) was examined. Although adjusted observations indicate the diets to have greater influence than apparent when unadjusted observations are used (**Fig 34** and **Table 31** in **Annex 47**, and **Fig 35** in **Annex 48**), the duration of treatment hardly 'explained' the variability between studies of different duration.
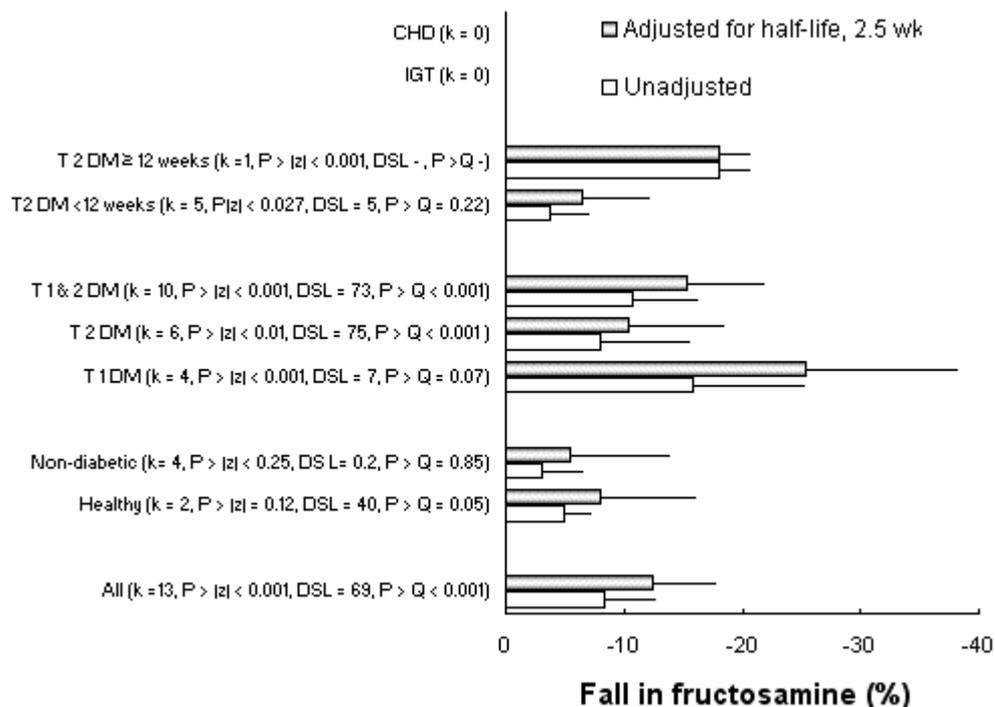
Fig 34: Combined means and study population 95% confidence intervals for treatment differences in fructosamine concentration by health type and duration. Abbreviations are: CHD risk of primary coronary heart disease; IGT, impaired glucose tolerance; T2DM, type-2 diabetes mellitus, T1DM, type-1 diabetes mellitus; k, number of studies (zero when no studies published prior to 2005); P > |z|, probability based on the z-score for a statistical significant difference from zero; DSL , Der Simonian and Laird estimate of between studies variance (%.%) (- given when too few studies published prior to 2005 to enable calculation), and P >Q, probability of significant among-studies variation based on the Q-statistic, with degrees of freedom = k-1.

Dietary composition

Earlier it was found that both the glycaemic character and the unavailable carbohydrate content of diets interact with the severity of abnormality in fasting blood glucose to explain the treatment effect size on fasting blood glucose. A possibility this occurs also for the effect size on fructosamine is examined (**Table 32** in **Annex 49**). As a 'deterministic' model, the simplest appears to be the most explanatory and relies on severity of abnormality in fasting blood glucose alone (Tau^2 is least when severity, S, is used even without these dietary characteristics). However, severity of fasting glucose is

expected to be permissive rather than causative of the effect, with possible causation being due to either more unavailable carbohydrate or lower glycaemic response to diet. The effects sizes for glycaemic character and unavailable carbohydrate are most readily compared when they have the same units (UC vs. GL or UC vs. AC-GL). Parameter estimates for the effect size on fructosamine when interacting with 'severity' indicate a greater effect (sensitivity or slope) for unavailable carbohydrate than for these glycaemic characteristics, an observation that is consistent with the earlier find for effect on fasting glucose. Although the findings are consistent for effects on fructosamine and fasting glucose, confidence surrounding the unavailable carbohydrate effect on fructosamine does not reach conventionally acceptable levels.

Possibly due to too few studies or for the need of studies of longer duration with HbA_{1c} than with fructosamine, no evidence similar to that above for fructosamine and fasting blood glucose arose to indicate dose dependency. This was the case for any mode of expression of the glycaemic character affecting either HbA_{1c} alone or for all measures of glycated protein combined, with or without adjustment for half-lives.

Health types

Among 13 studies combined from all health categories there is a highly significant fall in fructosamine due to treatment with lower than higher glycaemic carbohydrate diets of variable unavailable carbohydrate content (see lowest row in **Fig 34**). This applies also to all studies with diabetes mellitus patients combined, but not to studies of all non-diabetics combined or to studies of all healthy people combined. There are no studies prior to 2005 in either those at risk of CHD or those with impaired glucose tolerance. Statistically significant falls in fructosamine concentration in both type-1 diabetes (approx 20%) and type-2 diabetes (approx 10%) are evident. In the type-2 diabetics a substantial influence is attributable to a single study of longer than 12 weeks duration (**Fig 34**). Among health categories showing

statistically significant reductions in fructosamine there is generally significant heterogeneity among studies.

Prior to Jan 2005 more studies report on HbA_{1c} (k=19) than on fructosamine (k=13). Again in all studies combined there is a statistically significant lower HbA_{1c}, but due only to a significant effect in type-2 diabetics. The effect size at ≥12 weeks duration is similar to that found at ≤12 week (**Fig 35** in **Annex 48**). In contrast to a large decrease in fructosamine concentrations in type-1 diabetics (**Fig 34**) there is a smaller non-significant effect on HbA_{1c} (**Fig 35** in **Annex 48**). This difference is not attributable (with the present data) to differences in the duration of studies, meal numbers, differences in GI or GL or unavailable carbohydrate intake. Difference in compliance to diets during early periods and periods prior to analysis at the end of the study is a possible factor.

Study numbers on glycated protein are larger when combining observations on fructosamine and HbA_{1c}. There are significant effects in both type-1 diabetics (**Fig 36**) and type-2 diabetics (**Fig 37)**. Differences between type-1 and 2 diabetics are not significant when data are combined in this way, rather, difference found appear to be explained by differences in severity of abnormality in glucose homeostasis (**Fig 38**).

Fig 36: Random effects meta-analysis of glycated protein (fructosamine, HbA_{1c} or mean of fructosamine and HbA_{1c} where both are measured) in type-1 diabetes published prior to 2005. Data (boxes) are study mean treatment differences (ΔT) and 95% confidence intervals between low and high glycaemic carbohydrate diets expressed as a percentage of the mean of the two treatments (%MT). Box areas show relative study weights, by inverse variance. The diamond shows the combined mean (-9.2 %MT) and its 95% confidence intervals (-14.3 to -4.1, P>|z| = 0.001). The Der Simonian and Laird estimate of between studies variance was 20%% (P>Q = 0.05). Data shown are unadjusted for the half-life of fructosamine and HbA_{1c} and are identified by short-citation (first author, an abbreviated year of publication). Studies with one meal per day were excluded. Studies of short duration were not excluded, adjustments for half-lives of 2.5wks and 4.5 wks for fructosamine and HBA_{1c} yielded a combined mean of -13.7% (-22.6 to -4.9, P>|z| = 0.001) and indicated a Der Simonian and Laird estimate of between studies variance of 75%% (P>Q = 0.008).
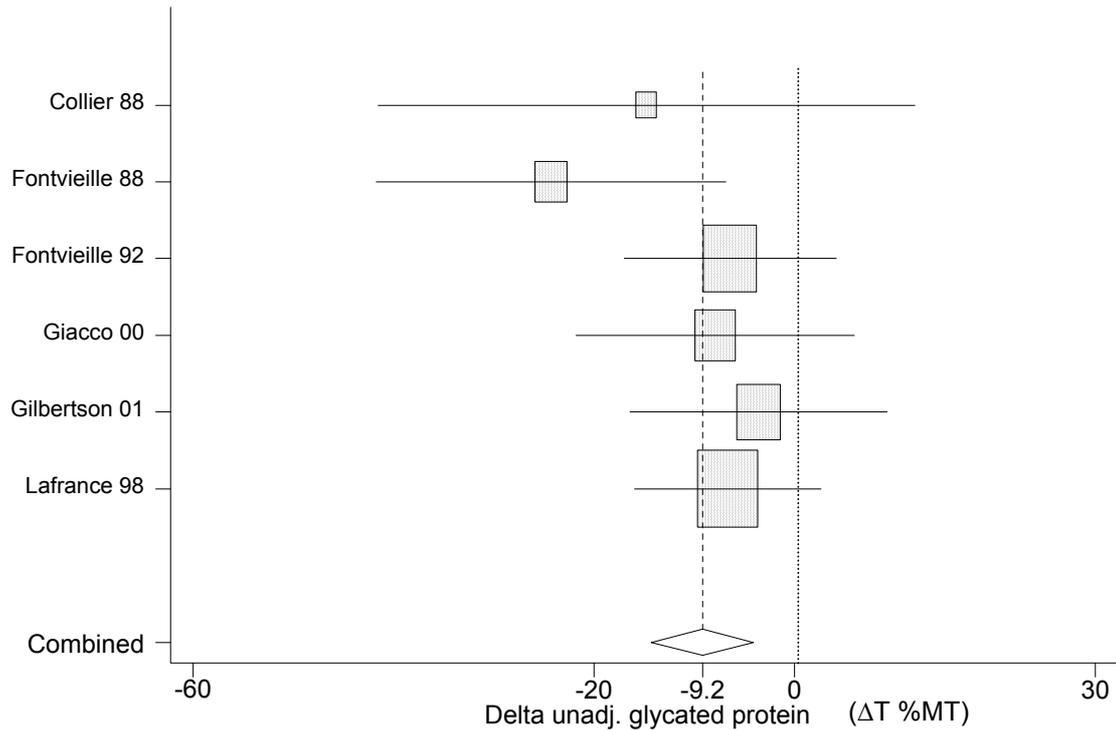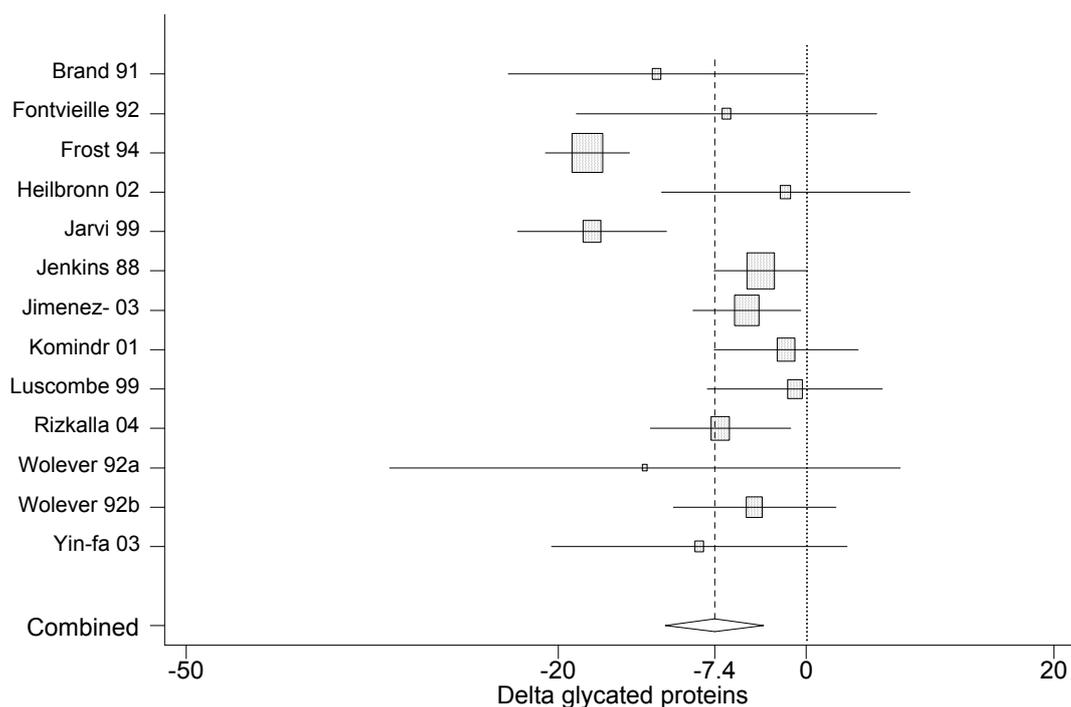
Fig 37: Random effects meta-analysis of glycated protein (fructosamine, HbA_{1c} or mean of fructosamine and HbA_{1c} where both were measured) in type-2 diabetes published prior to 2005.

Data (boxes) are study mean treatment differences (ΔT) and 95% confidence intervals between low and high glycaemic carbohydrate diets expressed as a percentage of the mean of the two treatments (%MT). Box areas show relative study weights, by inverse variance. The diamond shows the combined mean (-7.4 %MT) and its 95% confidence intervals (-11.34 to -3.7, P>|z|<0.001). The Der Simonian and Laird estimate of between studies variance was 42% (P>Q<0.001). Data shown are unadjusted for the half-life of fructosamine and HbA_{1c} and are identified by short-citation (first author, an abbreviated year of publication). Studies with one meal per day were excluded.

Studies of short duration were not excluded, adjustments for half-lives of 2.5wks and 4.5 wks for fructosamine and HBA_{1c} yielded a combined mean of -12.6% (-18.3 to -6.9, P>|z| = 0.001) and indicated a Der Simonian and Laird estimate of between studies variance of 83%% (P>Q <0.001).
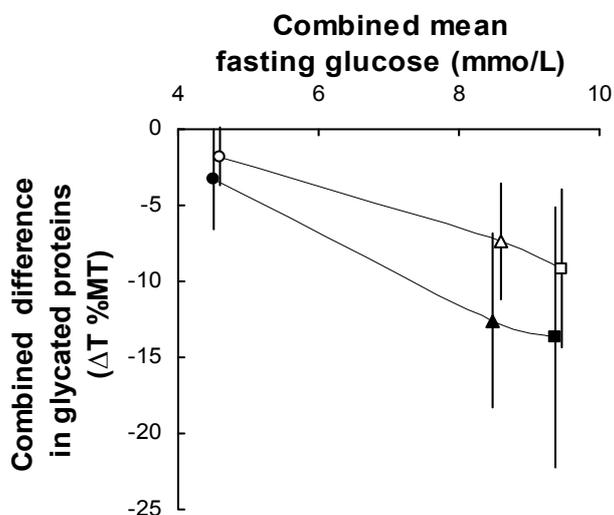
FIG 38: Treatment differences for combined glycated protein concentration in non-diabetics (○●), type-2 diabetes (Δ ▲), and type-1 diabetes (■□) before (○Δ□) and after (●▲■) adjustment for half lives.

Data are combined means from inverse variance random effects meta-analyses, and vertical bars are the 95% confidence intervals. Forest plots for type-1 and -2 diabetics without adjustments are shown at Fig 36 & 37).

Summary of findings:

i. There is strong evidence of a reversal in the abnormality in glycated proteins (fructosamine and HbA_{1c}) by consuming lower glycaemic variably higher unavailable carbohydrate diets (as found in diabetics).

ii. As with fasting blood glucose, the effect size of low-glycaemic variably higher unavailable carbohydrate diets is largest (in absolute terms) when the abnormality in fasting blood glucose is largest.

iii. Effects on fructosamine were consistent with those noted above for effects on fasting blood glucose; that is interaction with severity of the abnormality of fasting blood glucose, "dose-dependency" of glycaemic load (or index of load), greater sensitivity to unavailable carbohydrate than to glycaemic load (or index of load), and a fall in

fructosamine in diabetics (Type 1 and 2 combined), though little or no similar find in non-diabetics participants (for obvious reasons).

iv. Moderate reductions in glycated haemoglobin concentration are evident, however this evidence is weaker than for fructosamine and both are much weaker than for fasting blood glucose.

v. Adjustments of effect sizes for both fructosamine and HbA$_{1c}$ for corresponding half-lives for their turnover indicated studies to have underestimated the effect size overall.

vi. Using combed information on fructosamine and HbA$_{1c}$ as a single measure of 'glycated protein' a threshold of $\approx$ 5 mmol/L glucose or less was found above which low-glycaemic (variably higher unavailable carbohydrate) diets were effective, and for which the effect size was related to severity of abnormality in fasting blood glucose.

vii. A difference between all type-1 diabetics combined and all type-2 diabetics combined was small for the combined measure of glycated protein. The difference seen is ascribed to chance differences in severity of abnormality in fasting glucose concentrations.

viii. Studies were not indicative of low glycaemic (variably higher unavailable carbohydrate) diets having significant influence on H$_B$A$_{1c}$ concentrations in type-1 diabetics. This was a curious finding given that both fasting blood glucose and fructosamine were improved by these diets. Too few studies, too short duration of study and measurement problems cannot be excluded as explanatory.

Fasting Insulin

Dietary methods difference

Over all studies, no effect was seen at low fasting insulin concentrations (<100 pmol/L; **Fig 39** and **Fig 40**). Three observations at high insulin concentrations gave some indication of low glycaemic carbohydrate diets leading to relatively lower fasting insulin concentrations. One such study was a repeat of measurements in the same subjects according to a different study design over a different duration of treatment.
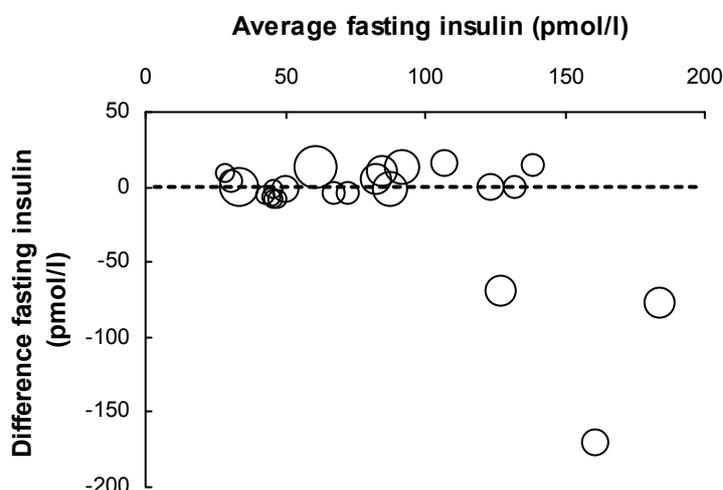
Fig 39: Dietary methods differences plot for all available data to 2005 on fasting insulin, low glycaemic carbohydrate treatment less high glycaemic carbohydrate treatment. Bubbles show the relative size of each study (√n) for 18 studies with 5 repeats (totalling 23 bubbles).

Overweight and obese

The responders (those who show relatively lower fasting insulin on a lower glycaemic diet) are overweight or obese and susceptible to fasting hyperinsulinaemia on the high glycaemic carbohydrate diet while maintaining normal fasting glycaemia. They include males in one study and females in another. Diets were maintenance in one study and sub-maintenance in another. Responders had received low glycaemic diets that were also higher in unavailable carbohydrate; it was not possible to assign cause to one rather than the other of these dietary characteristics. Being overweight or obese

alone was not sufficient to indicate responsiveness of fasting insulinaemia to a low-glycaemic carbohydrate (high unavailable carbohydrate) diet (**Table 33** in **Annex 50**). Where insulinaemia responded, it was towards relatively higher levels on introduction of a high-glycaemic carbohydrate low unavailable carbohydrate diet rather than restoration of normal insulinaemia with a low-glycaemic diet. Additional studies are essential to establish the circumstance and reproducibility of this potentially important physiological response.
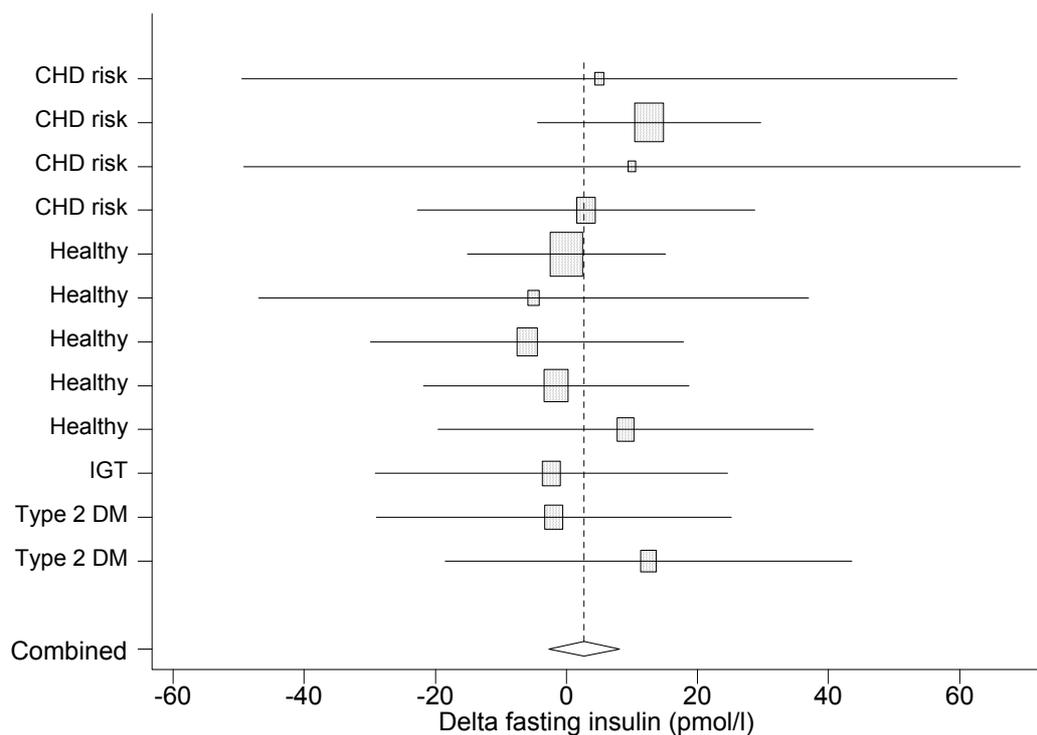
Fig 40: Random effects meta-analysis of treatment differences for fasting insulin <100pmol/L and studies prior to 2005. Observations are study means and 95% confidence intervals. Summary effects are shown in Table 33 in **Annex 50**.

Type-2 diabetes

Among five studies with type-2 diabetics, none of whom were using exogenous insulin, treatment had minimal and statistically non-significant impact on fasting insulin. Treatments comprised variable though consistently lower glycaemic carbohydrate diets simultaneously with variable and sometimes no different unavailable carbohydrate content. It was possible to associate lower-glycaemic carbohydrate diets in all five studies with no effect. There was too little information to draw conclusions about an influence or lack of influence of unavailable carbohydrate in these studies.

Summary of findings:

i. There is good evidence of no change in fasting insulin concentrations in studies combined from healthy participants, participants with glucose intolerance, participants at risk of CHD and patients with type-1 and 2 diabetes when fasting concentrations are below 100 pmol/L. This lack of effect occurs in people with reduced glycaemic load or index; there is too few data to assess a lack of effect of unavailable carbohydrate in this context.

ii. There is some evidence of a reduction in fasting insulinaemia due to ingestion of low relative to high glycaemic carbohydrate diets when the fasting insulin concentration is above 100 pmol/l; however, this evidence is weak due to few studies, for which there are two, one in overweight and one in obese participants. Neither study included diabetics.

Insulin sensitivity in pre-diabetics

Preamble

In general terms insulin sensitivity is another way of saying without insulin resistance. By Jan 2005, eighteen relevant studies either reported on insulin sensitivity using a range of different methods or provided post-prandial information from which this could be assessed. Among these studies observations were from healthy (k = 5) or glucose intolerant (k = 2) or type-1 (k =1) and type-2 (k = 5) diabetics or subjects at risk of primary or secondary coronary heart disease risk (k = 5). Principal methods used (some studies used more than one method) included the euglycaemic hyperinsulinaemic clamp technique, the insulin tolerance test, the frequent sampling intravenous glucose tolerance test, erythrocyte insulin binding, and the inverse post-prandial homeostatic model assessment method (inverse HOMA PP). Some studies reported assessments using more than one method. These provided additional information and were based on the inverse post-prandial HOMA and the sensitivity to insulin of glucose consumption by human adipocytes *in vitro*.

Dietary methods difference (low GI versus high GI)

In view of the large number of different methods used to assess insulin sensitivity it was not possible to generate a dietary methods difference plot. However, differences in sensitivity as a percentage of the average insulin sensitivity would indicate that low compared with high glycaemic diets (together with variable increases in unavailable carbohydrate) result in a statistically significant improvement in insulin sensitivity after combining results from all the studies (**Fig 41** and **Table 34** in **Annex 51**). Heterogeneity was statistically significant for the combined observations (**Table 34**). Separating these studies different ways into independent groups, by health or health risk (**Table 34**), by body weight class (**Table 35** in **Annex 52**), by method of assessment (**Table 36** in **Annex 53**), and by duration of study (**Table 37: Annex 54**) each show category mean increases in insulin sensitivity >0%.
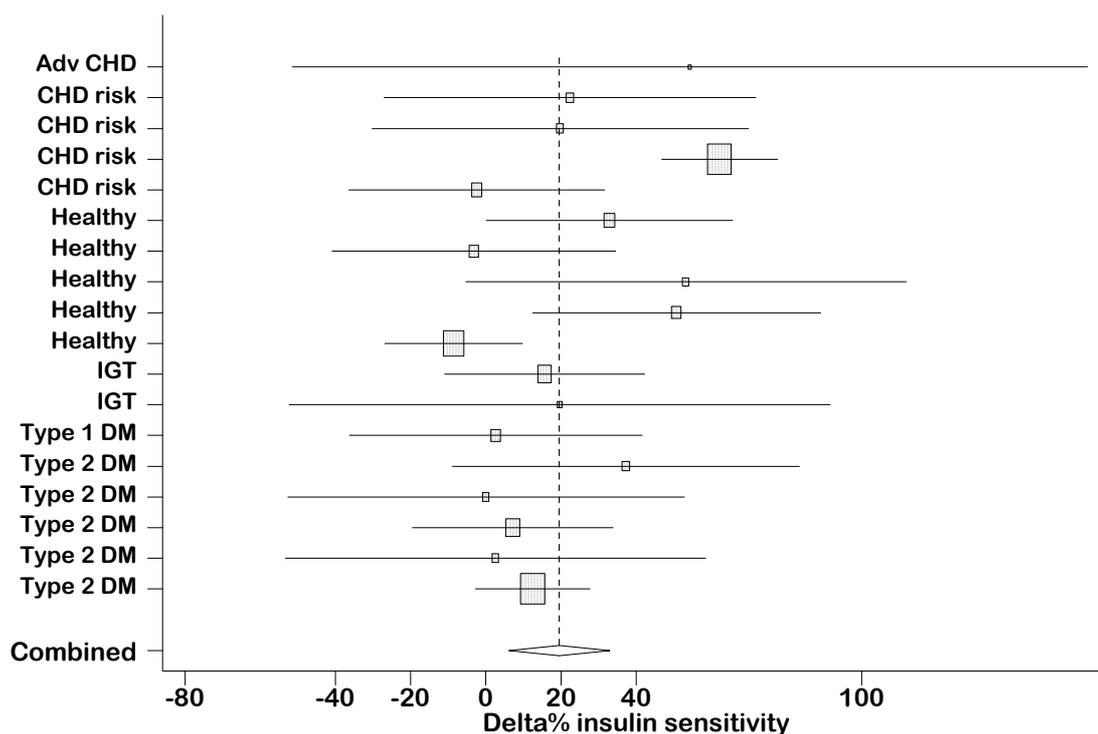
Fig 41: Random effects meta-analysis of insulin sensitivity (combining various health types, weight classes, duration of treatment and measurement methods) after treatment with diets of variably lower glycaemic and variably higher unavailable carbohydrate content. Results are given elsewhere by health type (Table 34), by weight class (Table 35), by duration of treatment duration (Table 36), and by method of measurement (Table 37). For sources see **Annex 54**.

All studies

Combining all eighteen studies indicates an 18% improvement in insulin sensitivity due to treatment with low glycemic carbohydrate diets of variable higher unavailable carbohydrate content, and is statistically significant (P=0.005).

Healthy individuals

Five studies categorised as healthy by the original authors' criteria indicate a combined mean rise of 20% in insulin sensitivity, which is no different to the mean rise for all studies, though this is not statistically significant (**Table 34**) by chance or due to too few studies.

TABLE 34: Summary of fixed and random effects[1] meta-analysis for treatment differences in insulin sensitivity.

Conditions	k (df) [2]	Combined mean effect (%rise)	95% CI for the mean	P>|z|	Q [3]	Hetero-geneity P>X [3]	DSL variance (%.%)[1]
All studies	18 (17)	20	6 to 33	0.004	78	0.001	563
All non diabetics (ostensible healthy)	12 (11)	24	4 to 44	0.014	68	0.001	879
Healthy	5 (4)	22	-5 to 49	0.11	20	0.001	724
Impaired glucose tolerance	2 (1) [4]	16	-4 to 36	0.11	-[4]	-	-
Type-2 DM	5 (4)	12	2 to 22	0.014	1.4	0.65	0
Type-1 DM	1 (-) [4]	3	-28 to 33	0.87	-[4]	-	-
1º and 2º CHD risk	5 (4)	29	-3 to 63	0.08	22	0.001	1049

1   All analyses were conducted with random effects, data report random effects when the Der Simonian and Laird estimate of between studies variance is >0 otherwise data report fixed effects.

2   Shows k number of studies and df degrees of freedom.

3   Q-test for heterogeneity and its significance, heterogeneity P greater than chi-square. Too few studies (<3) were undertaken to warrant providing full data from meta-

4   analysis (random effects assumed).

All studies without diagnosed disease

Participants without disease might be considered healthy, though not necessarily representative of the population of healthy people. Twelve studies indicate a combined mean improvement of 24% in insulin sensitivity, which would be significant as a primary or secondary question (2P>|z|=0.028) (**Table 34**).

Impaired glucose tolerance

The single study of impaired glucose tolerant participants indicated a 20% improvement in insulin sensitivity, which again did not reach statistical significance. Information about heterogeneity in this group is not available since there are too few studies to assess.

Diabetes

Improvement in insulin sensitivity in type-2 diabetes is about 10%, and would be significant as a primary question (P = 0.014; **Table 34**) though perhaps is non-significant given the higher chance of finding some effect when dividing all studies to 5 health groups (5P = 0.07).

There is no improvement indicated from the single study investigating type-1 diabetics (**Table 34**).

Coronary heart disease

Improvement in insulin sensitivity in primary and secondary CHD risk groups combined is about 29%, though as a primary question this is not statistically significant (P = 0.08) and is even less significant given the division of all observations to the five independent health groups (5P = 0.40).

Normal weight groups

Combining all health categories, a combined mean of 27% improvement in insulin sensitivity was observed in those of normal body weight (BMI <25 kg.m^{-2}), though this was not significant as primary question (P = 0.21) (see **Fig 42** below and **Table 35 in Annex 52**).
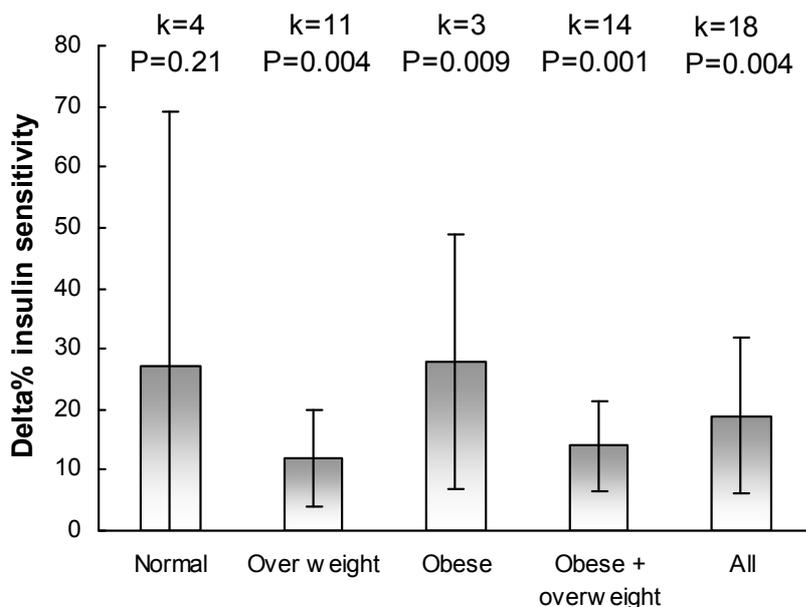
Fig 42: Random effect combined means and standard errors for differences in insulin sensitivity due to treatment with variably lower glycaemic and variably high unavailable carbohydrate diets in humans of different health types, results by body weight class. Studies are prior to 2005, including studies with healthy, impaired glucose tolerance, type-1 diabetes, type-2 diabetes, primary and secondary coronary heart disease risk whether normal weight, overweight or obese and by various methods of measurement of insulin sensitivity (see Tables i34 & 35).

Overweight groups

Combining all health categories, a combined mean of 12% improvement in insulin sensitivity is indicated. This was significant either as a primary question (P = 0.004) and after taking into account the division to three body weight categories (3P = 0.012) (**Fig 42** above and **Table 35** in **Annex 52**).

Obese groups

The improvement in insulin sensitivity in the obese individuals appears to be twice that in the overweight groups, and was 28%. The effect is statistically significant as either a primary question (P = 0.009) or after consideration of the multiple weight categories (3P = 0.027) (**Fig 42** above and **Table 35** in **Annex 52**).

Overweight and obese groups combined

Combining data from overweight and obese groups indicates a highly significant effect as a primary question (P=0.001) or after consideration of multiple categories (normal and overweight plus obese) (2P = 0.002) (**Fig 42** above and **Table 35** in **Annex 52**).

Duration of study

For combined health categories, there are 4 studies of duration 12 or more weeks and 14 studies of less than 12 weeks. The combined random effects mean insulin sensitivity is higher in both the longer term (16%) and shorter term (20%) studies, though this is statistically significant in the short term (P = 0.015, 2P = 0.030) it is less significant statistically in the long-term (P=0.11, 2P= 0.22) (**Fig 43** below and **Table 36** in **Annex 53**).
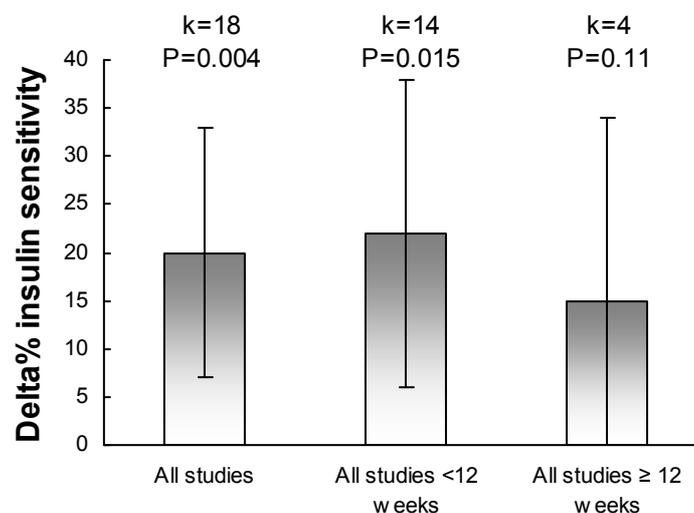
FIG 43: Random effects combined means and 95% confidence intervals for insulin sensitivity on treatment with variably lower glycaemic and variably high unavailable carbohydrate diets, results by duration of treatments. Studies are prior to 2005, including studies with healthy, impaired glucose tolerance, type-1 diabetes, type-2 diabetes, primary and secondary coronary heart disease risk whether normal weight, overweight or obese and by various methods of measurement of insulin sensitivity (see Tables 34 & 35 in Annexes 51 and 52 respectively).

Method of assessing insulin sensitivity

Among the 18 studies providing insight into insulin sensitivity, six assessed insulin sensitivity by more than one method or provided information from which to calculate insulin sensitivity by another method.

Eight studies provided information on post-prandial area under the total curve for circulatory glucose and insulin concentrations from which the inverse HOMA PP provides an assessment of insulin sensitivity (HOMA PP is an assessment of insulin resistance). The combined mean indicates a 30% improvement (**Table 37** in **Annex 54**).

Five studies indicate a value for HOMA S (or the inverse of HOMA R) that in contrast to inverse HOMA PP in the post-prandial state uses fasting glucose and insulin concentrations. Improvement in insulin sensitivity was 13%, though was not statistically significant (**Table 37** in **Annex 54**).

Three studies used the 'gold-standard' euglycaemic hyperinsulinaemic clamp technique; the combined mean of 7% improvement was not statistically significant (**Table 37** in **Annex 54**).

Three studies provide information from adipocytes ex vivo. Heterogeneity in results is marked and overall there is no statistical significant effect (P = 0.21). The combined mean is however consistent with the majority of in vivo assessments, showing an improvement in this case of 35%, with significant heterogeneity (P = 0.001) in results from different studies (**Table 37** in **Annex 54**).

Dietary characteristics

An examination is made of whether variation in the effect size for insulin sensitivity associates with variation in dietary characteristics related to carbohydrate (**Table 38** in **Annex 56**). A rise in either glycaemic index or glycaemic load appears associated with significantly poorer insulin sensitivity (P>|kh-t|<0.05). In contrast, the rise in either available carbohydrate or unavailable carbohydrate, while tending towards improved insulin sensitivity, is not statistically significant. Glycaemic load was not unique, replacing glycaemic load with the available carbohydrate less glycaemic load also yields a significant result. Likewise, indexing of glycaemic load to available carbohydrate intake was not unique. Thus indexing to the sum of available and unavailable carbohydrate or the sum of total carbohydrate plus protein gave similarly significant results. Further, indexing the sum of the glycaemic load and fat intake to the intake of organic mass (sum weight of available and unavailable carbohydrate, protein and fat intakes) yields a significant result.

In all these assessments the between-study variance (Tau^2) is significant indicating random effects analysis is appropriate. Variation among studies is remarkably high and accounts for approx 85% of total variation. Simultaneous use of unavailable carbohydrate and glycaemic index or load as possible independent determinants does not reduce Tau^2 more than using GI, GL or AC-GL as individual determinants.

Summary of findings:

i. Combined results from eighteen studies indicated overall a significant 20% improvement in insulin sensitivity due to treatment with low-glycaemic (variably higher unavailable carbohydrate) diets.

ii. Similar observations were made in normal weight (27%), overweight (12%) and obese (28%) groups of mixed health types of participants, though observation from normal weight groups had confidence intervals wider than for any other group and an effect that was not statistically significant.

iii. The improvement in insulin sensitivity for mixed health types combined in studies ≥12 weeks was as good as that in studies of <12 weeks duration. However, with fewer studies the effect over the longer duration was not statistically significant.

iv. Although significant improvement in insulin sensitivity is indicated over all studies combined, evidence for individual health types was weak with no one-health type being associated with a statistically significant effect. However, combining all 12 studies without diagnosed disease indicates a significant $(2P>|z|=0.028)$ combined mean improvement of 24% (95% CI 4 to 44%).

v. The improvement in insulin sensitivity was weaker in diabetics (3 to 13 %) than in non-diabetics (16 to 29%). There was only one study in type-1 diabetes (3%).

vi. Among all studies combined, insulin sensitivity tended to rise (non-significantly) with increase in unavailable carbohydrate intake and fall (significantly) with rise in glycaemic load or any indices of glycaemic load tested.

vii. Glycaemic index of available carbohydrate is evidently not unique as a potentially useful 'measure' of the glycaemic response to diets in the context of improvement in insulin sensitivity.

viii. In addition to different health types, different assay methods are used for insulin sensitivity. After consideration of multiple comparisons, no one method yields statistically significant results for combined health types, three studies using the euglycaemic clamp yield a 95 % confidence interval from -5 to 30% improvement.

HOMA estimates of B-cell function, insulin sensitivity and glucose disposition

The HOMA model

Fasting plasma glucose (FPG) and fasting plasma insulin (FPI) concentrations can be transformed to parameters called HOMA S and HOMA B according to an homeostatic model assessment method (Wallace, Levy et al. 2004) and these in turn to a third parameter HOMA D. HOMA S is a parameter of insulin sensitivity of glucose disposal and is the inverse of HOMA R, which is indicative of insulin resistance. HOMA B is a parameter of the insulin secretory response by pancreatic B-cells and sometimes referred to an index of B-cell function. The overall effectiveness of the homeostatic system for glucose disposal depends on both effective insulin secretory function and sensitivity to insulin of tissues using the glucose, and is the product of HOMA B and HOMA S, here this is called HOMA D (a disposition index). These are related as follows in which FPG has units of mmol/L and FPI has units of mU/L.

$$\text{HOMA } R = \text{FPI} \times \text{FPG} / 22.5$$

$$\text{HOMA } S = 1 / \text{HOMA } R$$

$$\text{HOMA } B = 20 \times \text{FPI} / (\text{FPG} - 3.5)$$

$$\text{HOMA } D = \text{HOMA } S \times \text{HOMA } B$$

The HOMA quantities may be expressed as a percentage of standard normal values in which FPG is 4.9 mmol/L and FPI is 7.6 mU/L (53 pmol/L), when they are denoted HOMA %S or HOMA %B etc. Whereas these two parameters use fasting values for plasma glucose and insulin, another parameter described in the literature applies to post-prandial values, in which case post prandial area under the curve (auc) is used in place of fasting values as in HOMA PP, a parameter indicative of insulin resistance (and its inverse of insulin sensitivity) in the post-prandial period:

$$\text{HOMA PP} = \text{aucFPI} \times \text{aucFPG} \, / \, 22.5$$

The HOMA model has two forms, a simple linear interpretation of the homeostatic model (called HOMA 1) and a more complex non-linear interpretation (called HOMA 2, as given by the Oxford HOMA calculator). Here observations use HOMA 1 and are called retrospective estimates since values are calculated retrospectively from published information on fasting glucose and insulin rather than being HOMA scores derived by authors elsewhere.
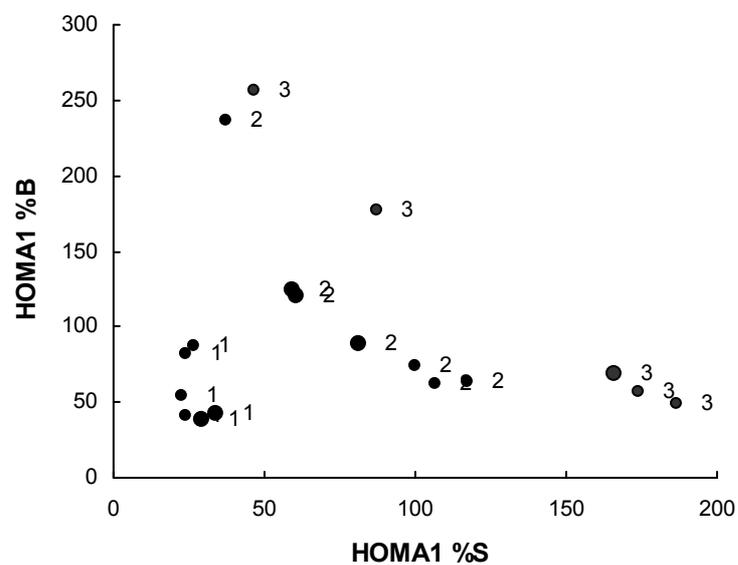
Fig 44: Categorisation of studies by HOMA %D (glucose disposition).

Values for HOMA %S (insulin sensitivity) and HOMA B (B-cell function) according to the HOMA1 model are treatment averages after treatments by variably lower glycaemic, (variably high unavailable carbohydrate) diets. On each scale 100% indicates a normal average. Category 1 is exclusively of type-1 and 2 diabetics. Categories 2 and 3 are each mixtures of normal, CHD risk, and IGT health types. Point areas indicate the size of each study in terms of the average number of participants per treatment ($\sqrt{n}$). HOMA %D is the product of HOMA %B and HOMA %S.

Interrelation of HOMA B, HOMA S and HOMA D

Among the low-glycaemic index and load studies identified prior to Jan 2005, seventeen (k = 17) give values of both FPI and FPG (or fasting blood glucose from which FPG is estimable). These comprise groups of healthy people (k = 6), groups with increased risk of primary of CHD (k = 4), groups with type-2 diabetes (k = 5), and groups with impaired glucose tolerance (k = 2). In addition, there was one study on type-1 diabetics for whom the HOMA model may not apply since insulin is under voluntary rather than homeostatic control. Among these study groups HOMA B and HOMA S vary over a wide range, though the groups fall into approximately three categories of differing HOMA D. The different categories of HOMA D are labelled here arbitrarily 1, 2 and 3 (**Fig 44**). Those studies in category 1 are of lowest HOMA B and HOMA S and are exclusively diabetic. Those in the remaining two categories are exclusively non-diabetic. It is supposed possible here that results of low glycaemic and high unavailable carbohydrate content may depend on the categories identified.

Dietary methods difference for HOMA B

The outcome of dietary treatments on HOMA B varies with the level of B-cell function experienced (**Fig 45** in **Annex 57**). There is however no significant difference between HOMA D categories when the meta-regression is structured for these categories to have different y-intercepts (slopes being forced to be the same for all categories).

Collectively, the low-glycaemic high-unavailable carbohydrate treatments elevated HOMA B when the average HOMA B was low but lowered it when mean HOMA B was high. Hence the low glycaemic high unavailable carbohydrate diets appear to have a normalising influence on B-cell function, pivoting about HOMA %B approx. 100.

This relationship is significant either forcing a combined constant (y-intercept) for HOMA D categories (P>|k-ht| = 0.001) or when allowing constants to differ for each category yielding three constants - one per HOMA D category as in

Fig 45 (P>|k-ht| = 0.004). It should be noted that statistical significance is dependent on high influence from sparse observations (k = 2) at high levels of B-cell function. Due to such sparse observations there is need to confirm or refute such a normalising influence on B-cell function by conduct of further studies.

Assuming the data to be reliable (i.e. new data would conform), low values of HOMA B would improve by 0.35% for each 1% fall in HOMA %B score (i.e. a 35% improvement, cuff the 30% improvement in fasting blood glucose shown above) (**Table 39** in **Annex 58**). The normalising influence is apparent even when adjusting for possible influence of variation in HOMA D or HOMA S (**Table 40** in **Annex 59**)**,** thus all models show a significant slope for HOMA B.

Non-diabetics

There is some evidence of normalisation, whether statistically significant or not in separate health categories: the healthy groups of individuals, groups at risk of CHD, and groups with impaired glucose tolerance (**Table 41** in **Annex 60**). Normalisation is most statistically significant for all studies combined and still very significant for all groups combined except diabetics.

Consistency of these observations among health categories is evident (**Fig 46** in **Annex 61**) though precise similarity is unclear due to too few data and HOMA %B covering different ranges of values in each health category. Nevertheless, estimates for each category fall within the 95% confidence interval for the mean value of all categories combined. No one category can be considered different from another. A possible exception is the type-2 diabetic group, for which it was necessary to force zero effect at HOMA %B = 100 to be in common with other health categories. The need for this may have arisen because type-2 diabetics with extremely poor B-cell function appear to not normalise as effectively as seen in other type-2 diabetics or other health categories.

Type-2 diabetes

Whether or not there is a normalising influence, low glycaemic high unavailable carbohydrate diets show via meta-analysis a significant (P>|z|=0.004; k = 5) improvement in HOMA B in type-2 diabetes (**Fig 47**) with a combined mean for all k = 5 studies of 12% improvement (**Table 42** in **Annex 62**).
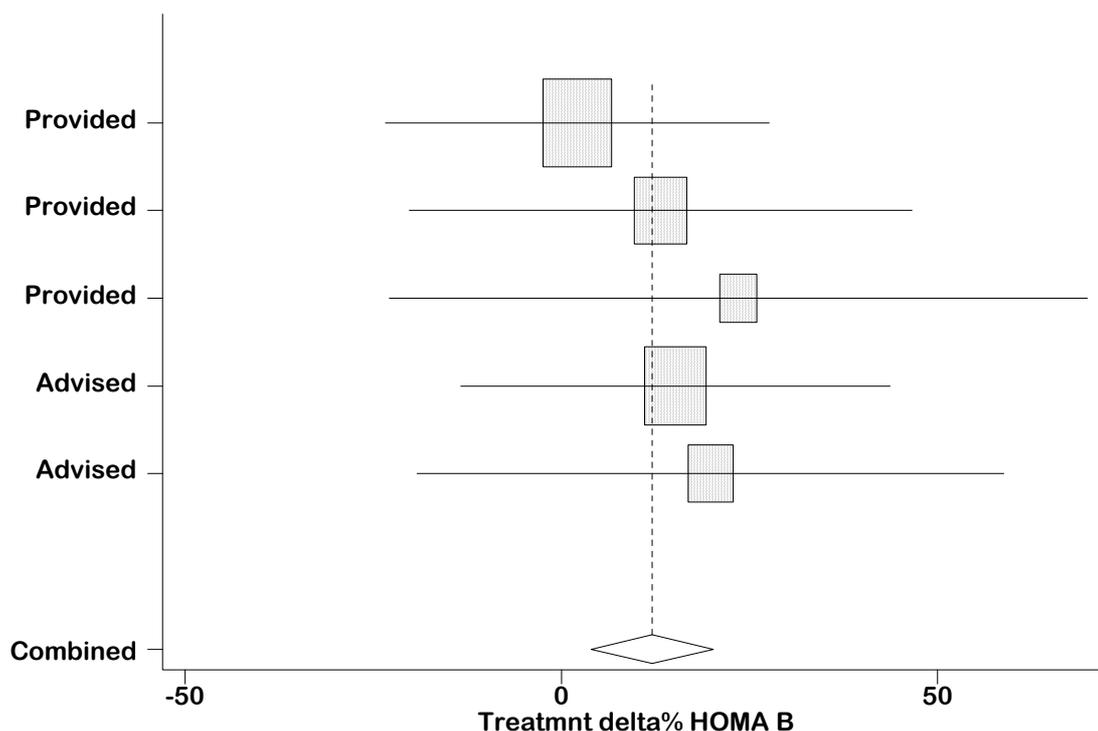
FIG 47: Meta-analysis of the retrospective HOMA %B response to variably lower glycaemic (variably higher unavailable carbohydrate) diets in studies of type-2 diabetics. Observations are for studies prior to 2005. The y-axis shows the method by which diets were administered, either some or all foods were provided or participants where advised about the foods they should consume The Der Simonian and Laird estimate of between studies variance is 0.000 (%.%) and the Q-test indicates significant heterogeneity (Q = 3.2, P = 0.52). The combined mean effect was +12.0 SEE 2.9, which differed significantly from zero (P>|z| = 0.004). See **Annex 63** for sources.

By contrast such a meta-analysis applied to studies in healthy people indicated no combined effect (**Fig 48** in **Annex 64,** and **Table 42** in **Annex 62**). The lack of effect here is attributed to a balance of the bidirectional influences.

The 12 % improvement of HOMA B in type-2 diabetics needs to be seen in context. In groups with a low HOMA %B, the lower the mean of treatments (MT) outcomes the smaller is the absolute effect for any given level of percentage improvement. An average improvement of 12 % in type-2 diabetes, with an average HOMA %B of 48% corresponds to a 6% improvement in more absolute terms (12 x 48/100). This improvement occurs during the average 4 weeks treatments. Since deterioration in HOMA B occurs on average at a rate of approx. 0.3% per month in type-2 diabetes (Wallace and Matthews 2002), the 6% improvement is perhaps equivalent to restoration of 1.5 years prior deterioration in B-cell function.

There is insufficient information on the time course for such improvement in B-cell function. Excluding a study of 3.5 weeks duration compared with 4 weeks for the other 4 studies in type-2 diabetics results in greater significance (P>|z|=0.001, k = 4) and effect, with a combined mean relative improvement of 17% (**Table 42** in **Annex 62**) equivalent to restoration of 2 years prior deterioration. Such improvement however might be better related to diet composition than to duration of treatment, in which case even greater improvement is potentially achievable.

Diet composition in type-2 diabetes

The lowest effect on HOMA B observed in type-2 diabetics occurs in a study in which there is no change in unavailable carbohydrate intake (Jarvi, Karlstrom et al. 1999). Only three studies report sufficient information to include an examination for a possible univariate association between effect size and treatment differences in unavailable carbohydrate intake, which is too small to draw conclusions (see **Annex 65** for more detailed information).

In each mode of expression of the glycaemic character of the diet the direction of effect (sign for sensitivity) is in the direction expected. However, due to the low number of studies such information might not normally be worthy of

remark. These observations, nevertheless, are consistent with the greater sensitivity of fasting glucose in type-2 diabetics to change in unavailable carbohydrate intake (in the context of a low glycaemic carbohydrate diet) than to change in the glycaemic character of the diet.

Severity of the condition and interaction with dietary composition

The value 'HOMA %B -100' gives here a measure of the departure in B-cell function from mid-normal (average healthy person) and is significantly related to the dietary treatment effect on HOMA %B (P > |kh-t| = 0.001).

Interaction between such departure from mid-normal and specified differences in dietary treatments among all studies is not evident however for GL, AC, GL/AC, AC-GL, or UC (data not shown). Lack of evident interaction may result from too few observations or absence of interaction.

Dietary methods difference for HOMA %D

A rise in HOMA %B is not automatically an indication of an overall improvement in homeostatic control of blood glucose concentrations, since it might be accompanied by a fall in insulin sensitivity of glucose disposal (increasing demand for insulin). Thus there exists a reciprocal relationship between HOMA %B and HOMA %S an index of insulin sensitivity (cf each category in **Fig 44**). The product of HOMA %B and HOMA %S divided by 100 yields an index here called HOMA %D, a rise in which suggests greater efficiency of glucose homeostasis.
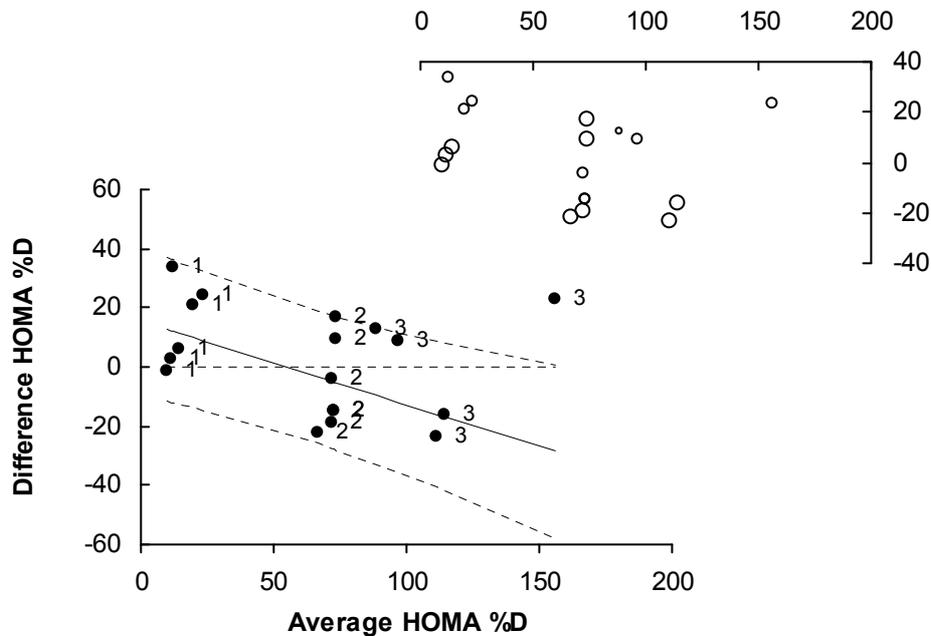
FIG 50: Dietary methods difference for HOMA %D response to variably lower glycaemic variably higher unavailable carbohydrate diets in all health types combined. Bubble areas shows the relative weights of each study (inverse variance) The data (k = 18 studies) are labelled by HOMA %D category (cf Fig. ha 1). Curves show the combined study meta-regression slope (——) and 95% confidence interval for the population of studies (-----). Given the outlying observation further studies are needed to establish or refute a significant relationship.

The treatment difference in HOMA %D expressed as a percentage of the treatment average in HOMA %D for type-2 diabetics indicates more probable improvement than not (**Fig 49** in **Annex 64**; P>|z| = 0.13; see also **Fig 50** category 1). Across all dietary treatments there was a weak trend for normalisation (**Fig 50**) (P>|kh-t|=0.2). This trend gained strength after truncation of observations at HOMA %D = 150, when P>|kh-t|=0.013 (**Table 43** in **Annex 67**). The observation removed had an influence statistic $\hat{B}_{ij}$ = 1.5, which being greater than 1 was reasonably removed.

Attributes of dietary carbohydrate and HOMA %D

There were too few data or too high variance or no significant trends to distinguish between the possible effects of low glycaemic carbohydrate (GI or GL) and unavailable carbohydrate, whether as univariate determinants or as

determinants interacting with departure from mid-normal (100%) in HOMA %D.

Dietary methods difference in HOMA %S

A rise in insulin sensitivity as indicated by HOMA %S following a lower glycaemic higher unavailable carbohydrate diet is seen only in individuals with low insulin sensitivity as indicated by HOMA %S (**Fig 51** in **Annex 68** and **Table 44** in **Annex 69**). This may explain some heterogeneity seen in results of the earlier, more direct, measures of insulin sensitivity.

Here, HOMA %S may be surrogate for HOMA %B with which it is related reciprocally. Substitution of the mean of treatment outcomes for HOMA %S with corresponding ones for HOMA %B gave a better fit to the treatment mean HOMA %S (**Fig 52** in **Annex 70**, and **Table 44** in **Annex 69**). Consequently, it appears that improvement in insulin sensitivity (HOMA %S) occurs most in those with good B-cell function (HOMA %B). This may explain why insulin sensitivity seen earlier by the more direct measures appears less affected in type-2 diabetics than in healthy people or those with CHD. A possible implication is that deterioration in insulin sensitivity would be better prevented than cured.

Since both HOMA %S and HOMA %B tend to normalise, changing in opposing directions with change towards low glycaemic higher unavailable carbohydrate diets, it is not surprising that the change in HOMA %S is inversely related to the change in HOMA %B (**Fig 53** below, and **Table 45** in **Annex 71**). These data clearly show influence of low glycaemic high unavailable carbohydrate diets in non-diabetic individuals, such as would be found among the regular population without clinical symptoms of disease.
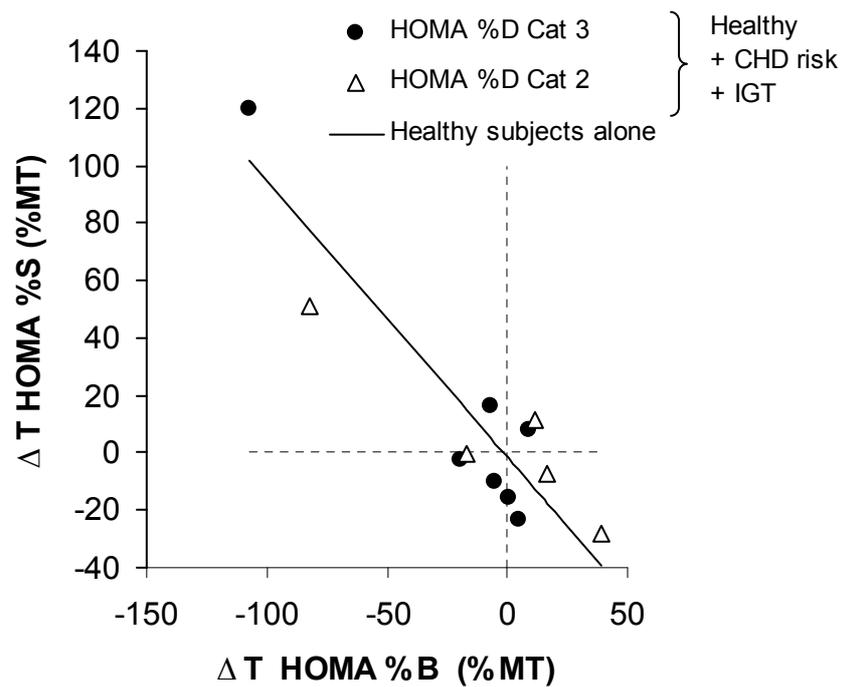
FIG 53: Inverse relation between change in insulin sensitivity and change in beta-cell function in non-diabetic individuals as indicated by the retrospective HOMA 1 model following in response to variably lower glycaemic variably higher unavailable carbohydrate diets. Data are for HOMA %D categories 2 and 3 (see legend). The inverse variance meta-regression line for studies of healthy people is also shown, and excludes those with IGT or risk of CHD (k remaining = 6 studies). The bubble plot (insert right) shows the relative weights (inverse variance).

Summary of findings:

i. Combining studies from all health types, the influence of lower glycaemic variably higher unavailable carbohydrate diets on B-cell (insulin secretory) function appears bidirectional, pivotal at a 'threshold' value for HOMA %B of 100, and so is normalising this physiological parameter. Within the duration of treatment there was an approximately 35% restoration towards a central norm.

ii. The normalising effect was evident most strongly in studies of non-diabetics combined. A low HOMA %B score in type-2 diabetics meant that bidirectional normalisation could not be established. Nevertheless the combined mean improvement in B-cell function in type-2 diabetics was significant, and at 12% is several times the rate of deterioration commonly experienced for this condition.

iii. Weak (narrative) evidence exits that improvement in HOMA %B in the type-2 diabetics is related to both unavailable carbohydrate and a lower glycaemic response, with sensitivity to the former possibly being stronger. This is would be consistent with the effect of these food characteristics on fasting blood glucose in type-2 diabetics.

iv. The improvement in HOMA %B in type-2 diabetics was accompanied by an improvement in the glucose disposition index HOMA %D; the strength of this effect is limited by the number of studies performed, with P= 0.11. A similar improvement in HOMA %D occurs across all health types combined, significantly (P<0.02) for HOMA %D values less than 150%

v. There are too few studies to attribute the effect of HOMA %D to either higher unavailable carbohydrate or lower glycaemic response.

vi. The retrospective estimates of HOMA %S also suggests bidirectional effects, with a rise in insulin sensitivity indicated at low values of HOMA %S and a fall in insulin sensitivity at high values of HOMA % S. However, the threshold or point at which the pivot occurs is ill defined, and possibly depends on HOMA %D, which implicates HOMA %B.

vii. Changes in HOMA % S and HOMA %B due to change in the glycaemic and unavailable carbohydrate character of diets are clearly inversely proportional in non-diabetics.

viii. In contrast with type-2 diabetics in whom an inverse association of HOMA %S and HOMA %B is muted, in groups of healthy people, people with impaired glucose tolerance, and people at risk of coronary heart disease the HOMA scores appear to respond readily to change in the glycaemic or unavailable character of the carbohydrate, with change in HOMA % S being strongly and inversely related to change in HOMA %B. An implication is that normalisation of HOMA scores to prevent type-2 diabetes would be easier than normalisation of these scores in established type-2 diabetics.

Fasting Triglyceride (triacylglycerol)

Preamble

Prior to 2005, 32 relevant studies were reported on fasting triglyceride concentrations. Among these studies, observations were from healthy (k = 7) or glucose intolerant (k = 1) or type-1 (k = 4) and type-2 (k = 15) diabetics or subjects at risk of primary coronary heart disease (k = 4) or a hyperlipidaemic (mixed categories, k = 1) groups of people. Six studies provided repeated observations (at 2, 2, 2, 2, 3, 4 time points) and one study provided information on four separate categories of hyperlipidaemia. These totalled 45 effect sizes.

Dietary treatment (methods) difference

There was no clear trend relating effects of a low versus high glycaemic variable higher unavailable carbohydrate diets on fasting plasma triglycerides that depended solely on the average fasting triglyceride concentration, although this concentration was always lower at the highest average fasting values (see **Fig 54**).

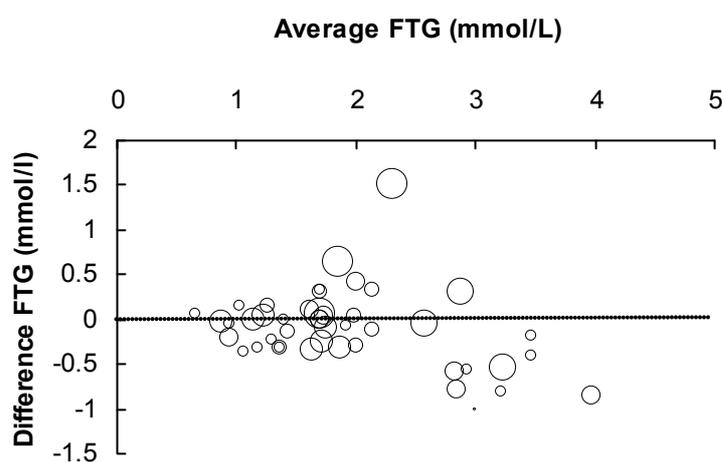**FIG 54:** Dietary methods difference plot of the fasting triglyceride response to variably low glycaemic (variably higher unavailable carbohydrate) treatment diets   Bubbles show the relative size of studies (√n) for 32 studies with nine repeats and four effect sizes from differing type of hyperlipidaemics considered here as one study (totalling 45 bubbles). Observations are from studies available prior to 2005.

Meta-analysis

For all 32 studies combined, having dropped intermediate data, the effect of low versus high glycaemic carbohydrate (variable unavailable carbohydrate) was mixed at the study level and with no effect overall (**Fig 55** in **Annex 72**). This was apparent whether for studies of less than 12 weeks duration or for 12 or more weeks (**Table 46** in **Annex 73**). There is also no significant treatment effect in any health category alone (healthy, CHD risk, impaired glucose tolerance, type-1 diabetes, and type-2 diabetes; each of mixed body weights) or body weight condition (normal, overweight, obese; each of mixed health category). A single study not reported separately in **Table 46** in **Annex 73** and finding a significant effect in hyperlipidaemics subjects (Jenkins, Wolever et al. 1987b) is not evidently a unique observation – several others show individual study means with upper 95% confidence intervals <0 mmo/L (**Fig 55** in **Annex 72**). The Q-test for **Fig 54**, which suggesting a lack of heterogeneity, is evidently conservative because visual inspection indicated significant effects of individual studies in the tails, so calling for an examination of the cause, here supported by meta-regression.

Meta-regression

Although no meta-analyses (above) shows significant effects of low versus higher glycaemic carbohydrate treatment in any health category or body weight condition (**Table 46** in **Annex 73**), this does not automatically mean that glycaemic character of the diet is without influence, coexisting counterinfluences may arise.

Inverse variance random effects meta-regression indicated trends for influence of various characteristics of the diet (**Table 47** in **Annex 74**). A weak or no trend occurs towards higher triglycerides with more carbohydrate (P>|kh-t|=0.13; 6P>0.9). A significant or weak trend occurs towards lower triglycerides with more dietary fat (P>|kh-t|=0.019; 6P>0.11). A strong significant trend (P>|kh-t|=0.003, 6P=0.018) towards lower triglycerides occurs with diets of low glycaemic load (**Table 47** in **Annex 74).**

The significant effects of change in fat intake and change in glycaemic load on fasting triglycerides remain when each of these two dietary characteristics are used in bivariate inverse variance meta-regression **Fig 56** and will be elaborated on below.

After adjustments for variation in fat intake, it appears not to matter among these studies whether the glycaemic character of the diet is expressed as GL alone or GL indexed in any of a number of different ways to other dietary components, though GL had the strongest association (**Table 48** in **Annex 75**). Also the relationship with fat intake remains apparent however glycaemic load is expressed or indexed (**Table 49** in **Annex 76**).
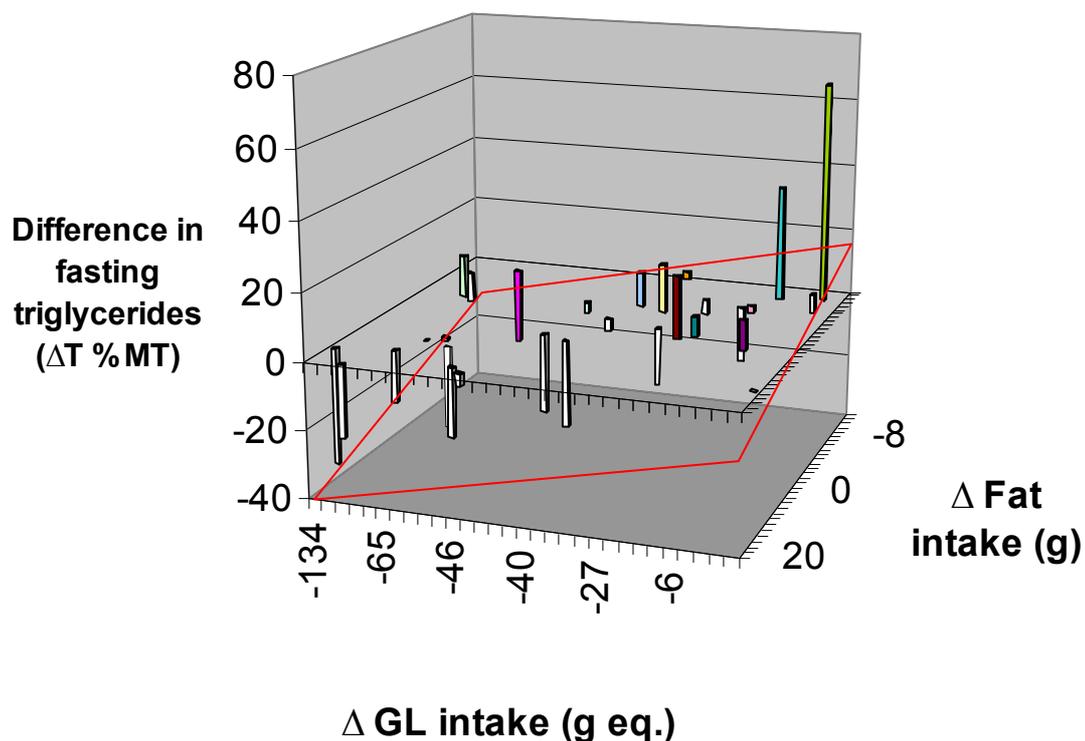
FIG 56: Bi-variate determinants of the effect size for difference in fasting triglycerides. The tilted quadrangle joins predicted points at each corner with straight lines for all 30 studies. Those studies showing a mean fall in fasting triglycerides are identified in white.

3

The rise in fasting triglycerides with rise in GL (after adjustment for fat intake) is observed in all studies combined and variously in different health types (healthy, type-1 diabetes, type-2 diabetes) and body weight (normal, overweight, obese) types (**Fig 57**). Although this rise is not statistically significant in any one of the health categories the influence is similar in direction in all, with each health type and bodyweight type contributing to the significance of effect over all the studies combined. Likewise there is a fall in
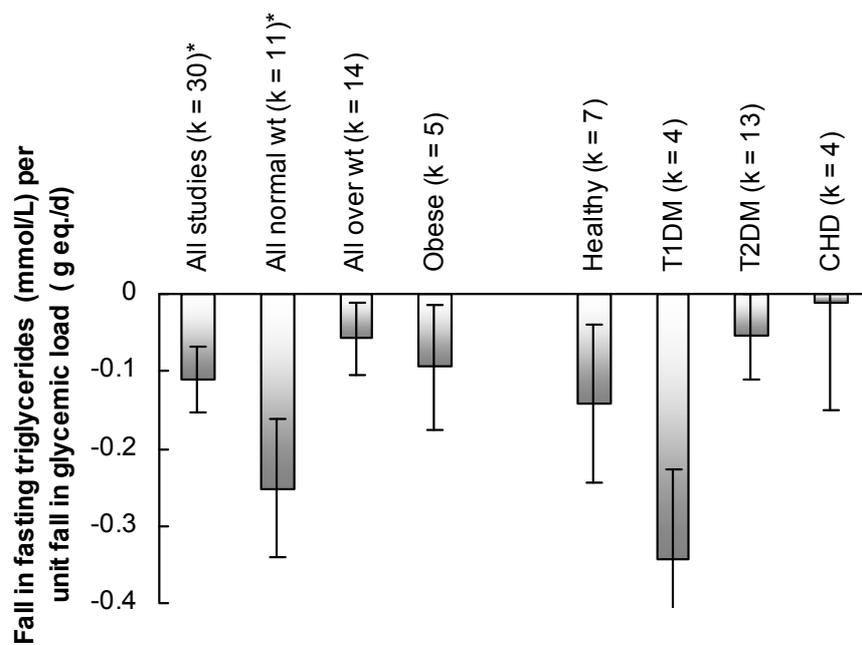
FIG 57: Rise in fasting triglycerides on rise in the glycaemic load after adjustment for fat intake, by body weight class and by health type. Data, the regression coefficients and standard errors of estimation derived by random effects multiple regression for the number of studies shown.

Severity of abnormality in triglycerides

When severity of abnormality of fasting triglycerides is considered to interact with the change in glycaemic load and change in fat intake there is moderate improvement in the prediction of effects on triglycerides. The effect of severity is not large, though as a determining interactant it increases the probability of effects of the parameters for change in glycaemic load and change in fat intake (**Table 50** in **Annex 77**). This implies somewhat greater effects of dietary change in people with higher levels of fasting triglycerides. Here severity was the treatment average triglyceride concentration. No improvement in the explanatory model arose from insertion of a threshold below which severity of fasting triglycerides could be considered without effect.

Summary of findings:

i. A simple meta-analysis of low glycaemic variable unavailable carbohydrate treatment failed to uncover a significant effect on fasting triglycerides. Such failure is attributed to bidirectional effects of dietary interventions on nutrient intake.

ii. Meta-regression by contrast indicates statistically significant effects due variation in fat intake (when less raises fasting triglycerides) and reduction in glycaemic load (when less lowers fasting triglycerides). After adjustment for fat intake, falls in several possible indices of glycaemic load (GI_{AC}, GI_T etc.) significantly associated with a fall in fasting triglycerides, though glycaemic load showed the strongest association.

iii. Variation in metabolisable energy, protein, available carbohydrate and unavailable carbohydrate did not contribute to these changes in fasting triglycerides either because of a lack of sensitivity to these dietary components or because variations in these components were too narrow to demonstrate effects.

iv. There was weak evidence of interaction between glycaemic load and severity of abnormality of fasting triglycerides, and between fat intake and severity of abnormality fasting triglycerides. However, there was no

evidence of a threshold in abnormality of fasting triglycerides that would improve prediction of the outcome of change in diet.

v. On average, a 1% fall in fasting triglycerides required a fall in glycaemic load of 7 g eq.

vi. While there is strong evidence of fasting triglycerides being related to glycaemic load over all studies after adjustment for fat intake, evidence of effects in each health type separately is weak. Nevertheless, similar even if non-significant rises in fasting triglycerides with rise in glycaemic load occurred in normal, in overweight, and in obese subjects. Similar weak effects were also found in healthy subjects and in patients with type-1 diabetes mellitus. Very weak or no effect was found in patients with type-2 diabetes mellitus or in patients at risk of coronary heart disease. These data might imply prevention of fasting triglycerides becoming abnormal might be preferable to attempts at correction.

Discussion

Meta-analyses and meta-regression analyses of intervention studies concerning the glycaemic response (glycaemic index and glycaemic load) are undertaken by query of a purpose built database of study results. The questions asked are far from exhaustive and readers are likely to have questions that are not answered.

Comparison of methods in the present and prior meta-analyses

Meta-analyses and regressions demand formal protocols. There is an anecdotal claim elsewhere to a presence in the literature of several met-analyses in the literature on glycaemic index and body weight, with citations of the examples of (Raben 2002) and (Pawlak, Ebbeling et al. 2002). To the present author's knowledge and following examination of the electronic databases herein used, there are no such prior formal treatments of the literature on glycaemic index or load and body weight prior to 2005 that meet criteria necessary for meta-analysis. The references offered to support the anecdotal claim provide the antithesis of a meta-analysis by taking sides in a debate (i.e. begin with bias and provide data in support of it).

Four formal or near formal meta-analyses have been published concerning glycaemic index health markers other than body weight. These differ in their approach to the present one in several ways. Three apply fixed effects analyses; two were concerned with diabetes (Anderson, Randles et al. 2004) (Brand-Miller, Petocz et al. 2003) and one was concerned with coronary heart disease (Kelly, Frost et al. 2004). As in the analyses at present, random effects meta-analysis has been used to assess the health effects of glycaemic response in regard both diabetes and coronary heart disease (Opperman, Venter et al. 2004). Here there is greater focus on dysglycaemia and physiology in health people, the role of unavailable carbohydrate, and attendant changes in macronutrient intakes, the latter to asses possible confounding.

Random and fixed effects analyses produce the same result when there is no between-studies variance. Whenever such variance is present the fixed effect analysis provides an overoptimistic estimate of significance of a treatment effect because it ignores the variation between studies. Acceptance of fixed effect models is considered reasonable whenever a Q-test (chi-square) 'shows' absence of statistically significant between-studies variation (i.e. when heterogeneity is found). However, this test is far from exact, is dependent on accuracy of the within studies estimate of variance of the treatment effect, and may lead to false negatives for real differences between studies.

Use is made at present of meta-regression to assess the possibility that variation between studies is related to co-varying factors. No prior review related to glycaemic response of foods is known to the author to have used this approach. This was considered important when combining results from diverse studies, such as from patients and non-patients in whom risk factors may vary continuously between health types. Also it was considered potentially important within a health type. For example, diabetes mellitus patients present with differing degrees of severity of the condition, among which risk factors vary continuously. A further reason for using meta-regression is that it provides a method to assess the sensitivity of an outcome to variation in more than one factor at a time, including otherwise potentially confounding variables.

Studies differ in their power to make an observation through using different numbers of participants, differing study design, and through there being differences in variation among factors of interest among the sampled populations. Consequently, studies are weighted to take account of these differences when determining the combined effect of similar on related studies in meta-analysis or meta-regression. The weighting differs between the present analyses and previous ones. Firstly, random effects analysis is used, which contributes between studies variation ≥0 to the weighting - here whether the random effect is statistically significant or not, whereas fix effect analyses consider only variation between participants within studies. Second, the within study variance in treatment effect is derived using information (r_p)

imputed from a maximum of studies included in the database and where evident it is time varying. One prior meta-analysis relied on a single study to assess r_p, which of necessity was time invariant (Brand-Miller, Petocz et al. 2003). Authors of the other meta-analyses either do not detail how they estimate dependent variance for differences between treatments (Anderson, Randles et al. 2004; Kelly, Frost et al. 2004) or appear to use variation in change score (standard error of difference in end value and baseline value) without making clear how cross-over and parallel designed studies were treated differently (Opperman, Venter et al. 2004). There is therefore a high risk of prior meta-analyses yielding biased estimates of heterogeneity.

The present estimates of heterogeneity are also not exact since estimation procedures were used in the derivation of dependent standard error differences between treatments. Calculation from P values given as 'less that' assumes a value of 'equal to', e.g. $P < 0.05$ assumes $P = 0.05$ for calculation purposes, as suggested previously (Deeks J, Higgins J et al. 2002), whereas P values would likely be between 0.02 and 0.05 (for which P values are commonly listed in tables). Consequently, heterogeneity is likely to be underestimated at present, the consequence of which is the derived statistical significance of treatment effects will be conservative, and studies of low precision will be marginally underweighted.

Study quality

Assessment of study quality and use of terminology surrounding study quality differ among the published meta-analyses. Studies categorised as having poor quality by some meta-analysts (Kelly, Frost et al. 2004) have also been categorised as having good methodology by others (Opperman, Venter et al. 2004). No overall categorisation of study quality was given elsewhere though certain limitations have been well discussed (Brand-Miller, Petocz et al. 2003; Anderson, Randles et al. 2004). Despite such differences the published meta-analyses and the present one assume all included studies to be of similar quality and so are similarly weighted in this particular.

The results of meta-analysis arise from 'compliant to treatment' analyses rather than 'intention to treat' analyses. Reasons give for participants dropping out, or supervisors dropping participants post randomisation are mostly related to personal circumstances and demand of the study, and least due to compliance to diet (see drop outs in the methods section).

Quality of dietary information

Information about diets is often assessed by reference to food composition tables. The studies on glycaemic response reviewed are no exception, though not exclusively. In general this could contribute to heterogeneity that is unexplained in either meta-analysis or meta-regressions. There are three important issues. Firstly, unexplained heterogeneity widens the confidence limits and underestimates the statistical significance of real relationships. Second, food composition tables and food labelling will always have inaccuracies, and their present state represents a worst case – improvement would be likely with better analytical methods and provision of food tables including local foods. Third, intervention trials based on direct analysis of the foods eaten in the study leave open the question of whether the observations made would be transferable to the real world of inaccuracies in food composition tables and labels. Nevertheless, scope exists for more accurate food tables and greater significance of relationships between glycaemic responses and markers of health.

Interrelation between glycaemic index, glycaemic load and unavailable carbohydrate in practice.

Particularly notable is a bitonic influence between available carbohydrate intake and glycaemic index. Evidence for this is strong, being statistically significant over all studies combined, with some evidence of occurrence in each food intake category, namely ad-libitum, limited control and even studies in which control over food intake and composition had been intended (**Fig 5** and **Table 3**). This is manifest as an initial jump in available carbohydrate intake that accompanies an even modest reduction in glycaemic index,

followed by a trend towards reduction in available carbohydrate intake as the glycaemic index is reduced further. The jump is presumably a response to the intervention (food choices) and not a response to the low glycaemic character of the diet (physiological effect). Due to this bitonic response, variation in glycaemic load among the studies reviewed is greater than would be expected from variation in glycaemic index alone. A part of the trend is a weight-for-weight exchange of available and unavailable carbohydrate, again statistically significant in all studies combined and evident to some extent in all food intake categories (**Figs 10** and **11**, and **Table 8**). Consequently, a difference in glycaemic load is predicted more precisely by a difference in glycaemic index of total carbohydrate than it is by a difference in glycaemic index of available carbohydrate (**Fig 9,** and **Table 6** and **7**).

Fat intake in response to reduced available carbohydrate intake

Although a jump and reverse trend in available carbohydrate intake arises across studies as the glycaemic index is progressively reduced, there is strong evidence of little compensatory rise in fat intake (**Fig 6**). Indeed, over all studies combined, the reverse trend lowering available carbohydrate intake (**Fig 5**) is accompanied by a trend towards a lower metabolisable energy intake. Such a trend is however stronger between glycaemic load and metabolisable energy intake (**Fig 12** and **Table 9**) than it is between glycaemic index intake and metabolisable energy intake (**Fig 3** and **Table 2**).

Glycaemic response and body weight change.

Consistent with a reduction in metabolisable energy intake, as glycaemic load is reduced there occurs a fall in body weight (kg/wk) that is also related to glycaemic load (**Fig 18**). This is evident in each food intake category except when intake is controlled (**Fig 19**). The relationship with glycaemic load emerges stronger than with glycaemic index (**Table 17**). There is insufficient information about dietary energy density to assess whether glycaemic load, energy density or a combination of these properties contribute to the body weight reduction found. Nevertheless, the body weight reduction associated

with glycaemic load is independent of fat intake, a major determinant of energy density. There is insufficient information to exclude possible differences in energy density due to variation in the water content of food.

Overweight and obesity

Obese and overweight individuals are at increased risk of metabolic syndrome and so diabetes and coronary heart disease. Risk factors include high body weight (fat), insulin resistance (or insensitivity), hyperglycaemia, hyperinsulinaemia, and hypertriglyceridaemia, amongst others.

Body weight reduction accompanying consumption of diets of variably lower glycaemic load with variably higher unavailable carbohydrate (i.e. through manipulation of total carbohydrate types) is evident at a low rate of change (**Fig 18**) but when it occurs it evidently may persist up to a year (**Fig 20**). The maximum rate of body weight loss (0.2 kg/week; **Fig 18**) corresponds to approx 10 kg per year more than seen in those receiving the control treatment. Such a maximum rate of loss (or lack of gain) corresponds to that found over the one year period (**Fig 20**). However, the evidence does not support with more than 95% confidence a body weight reduction of more than 2 kg. This also requires a reduction in glycaemic load of at least 50 g glucose equivalents daily, which compares with a range of change in GL of approx.150 g glucose equivalents achieved in the studies reviewed.

A relative fall in fasting insulin (on low-glycaemic variably higher unavailable carbohydrate diets) or rise in fasting insulin (on high glycaemic variably low unavailable carbohydrate diets) is observed in certain studies in overweight and obese groups (see results). This is consistent with a susceptibility of overweight and obese persons to hyperinsulinaemia (**Fig 39**). However, such a response is not observed in all studies with the overweight and obese. The circumstances of this effect remain to be elucidated.

Obese and overweight individuals also tend to be insensitive to insulin, predisposing or contributing to metabolic syndrome. There is weak evidence

of improvement in insulin sensitivity among all health categories combined whether normal, overweight or obese (**Fig 42**).

Obese individual are at greater risk of metabolic disease when fasting triglycerides are raised. There is weak evidence that fasting triglycerides are raised by high glycaemic variably lower unavailable carbohydrate diets relative to low glycaemic variably higher unavailable carbohydrate diets in all body weight categories (**Fig 57**). The present meta-analyses and regressions largely concern starchy foods though do not exclude those studies that include some fructose or sucrose as part of the diet to reduce the glycaemic response. There is some evidence that excessive levels of fructose may elevate fasting plasma triglyceride concentrations, while regular levels of fructose consumption improve both blood glucose control and possibly fasting triglycerides – consistent with its low glycaemic character (not reviewed herein).

Type-1 diabetes mellitus

The key goal in the management of type-1 diabetes is to lower fasting blood glucose to normal. Evidence indicates that type-1 diabetics respond to the present dietary treatment just as sensitively as do type-2 diabetics. Their response is evidently to the exchange of available and unavailable carbohydrate in addition to exchange of available carbohydrates of differencing glycaemic index (**Table 28**). This evidence is based on few studies (5) and so is seemly very weak. However, plausibility in type-1 diabetics does not stand on evidence from them alone, in that it is consistent with observations in type-2 diabetics, with significant observations in type-1 & 2 diabetics' patients combined, and with highly significant observations in all health types combined (**Table 28**). Among these studies, change in the unavailable carbohydrate content of the diet in the context of achieving a low glycaemic load was equally (dietary intake level) or possibly more important (g/g substrate) than change in the glycaemic character of the carbohydrate.

A useful reduction in any one risk factor without adverse influence on other factors is the minimum required for a dietary factor to be considered efficacious. Studies lowering the glycaemic index of diets in type-1 diabetics indicate a combined mean fall in fasting glucose by 1.5 mmol/l, and a 15 to 20% fall in fructosamine concentrations or 9% fall in combined glycated proteins (**Fig 36**).   No adverse effect on glycated haemoglobin or fasting triglycerides is evident, and there is either no effect or a reduced rate of hypoglycaemic events (see below). Evidence on insulin sensitivity in type-1 diabetics prior to 2005 is limited to one study, which indicates no adverse effect (see within **Fig 41**). Should a new stead state have been reached before the ends of these studies the low glycaemic carbohydrate diet could be considered helpful in the treatment of type-1 diabetes.

An absence of an overall treatment effect on triglycerides in type-1 diabetics is evident but does not mean insensitivity of this parameter to glycaemic index or glycaemic load in this health type. Such a result could arise from a balance between an 'intervention effect' acting to raise triglycerides, and a low glycaemic load effect acting to lower triglycerides. Meta-regression is consistent with covariance in triglyceride concentrations and glycaemic load, such that type-1 diabetics appear to be at risk of hypertriglyceridaemia due to high glycaemic diets as much as any other health type examined (**Fig 57**). The health message or dietary advice given to communicate the potential benefit of low glycaemic diets in respect of triglycerides in type-1 diabetics needs to be considered with aim to maximise this potential if benefits are to be achieved more consistently among patients.

Type-2 diabetes mellitus

Again, a useful reduction in any one risk factor without adverse influence on other factors is the minimum required for a dietary factor to be considered efficacious. In type-2 diabetics, low glycaemic high unavailable carbohydrate diets reduce fasting blood glucose (**Fig 29**), fructosamine (**Fig 34**), glycated haemoglobin (**Fig 24**), combined glycated protein (**Fig 37**), elevate

retrospective HOMA %B (**Fig 47**) and have no adverse effects on fasting insulin (**Table 33**) or triglycerides (**Table 46** and **Fig 57**).

Insulin sensitivity is improved (**Table 34**) but retrospective HOMA %S does not reflect this (**Fig 51** and **52** for HOMA %D category 1). The low quality of methodology used for assessment of insulin sensitivity, possible lack of sensitivity of the HOMA model to real changes, small number of studies, and small number of participants per study lead to an uncertain classification of the response of insulin sensitivity in these patents, either as a no adverse effect or as an improvement.

As with type-1 diabetics, the key goal in the management of type-2 diabetes is to lower fasting blood glucose to normal. Treatment of combined health types (all studies) with lower-glycaemic variably higher unavailable carbohydrate diets corrects the abnormally higher fasting blood glucose by approximately 30% (**Tables 20** to **22**). Such treatment is just as effective in type-2 diabetics alone and arises from change in both the glycaemic and unavailable carbohydrate in foods (**Table 28**). Change of the unavailable carbohydrate content of the diet in the context of achieving a low glycaemic load in type-2 diabetics was equally (diets level) or possible more important (per g UC or GL change) than change in the glycaemic character of the carbohydrate, both for the sensitivity of the fasting glucose response to the dietary change and for the strength of evidence (P value) (**Table 28**).

Coronary heart disease

Among patients categorised by authors as at risk of coronary heart disease, there was evidence of no adverse effects on fasting blood glucose (**Figs 29** and **31**), fasting insulin (**Figs 39** and **40**), retrospective HOMA %B (**Table 42**), and sensitivity of fasting triglycerides to change in glycaemic load (or index). Studies provided no evidence on fructosamine and glycated haemoglobin.

There is weak evidence for a favourable or marked response of insulin sensitivity to the low glycaemic variably higher unavailable carbohydrate diets

in those with an elevated risk of CHD (**Table 34**). There is also weak evidence of normalisation of pancreatic function HOMA %B (**Fig 46**), a finding for which there is stronger evidence among all health types combined, all non-diabetics combined, and all metabolic disease bar diabetics combined (**Table 44**),

Groups at risk of CHD also contributed to evidence for persons with fair to good glucose disposition (HOMA %D) responding to lower glycaemic-variably higher unavailable carbohydrate diets by normalisation of their HOMA %B and HOMA %S scores. This would imply less risk of progression to either type-2 diabetes or coronary heart disease.

A useful improvement in any risk factor without adverse effects on others would be a minimum for considering low glycaemic variably higher unavailable carbohydrate diets in the prevention or treatment of coronary heart disease. Among the major risk factors for coronary heart disease assessed here are overweight, reduced insulin sensitivity, hyperglycaemia, hyperglycation and hypertriglyceridaemia. Combining all health types shows all five risk factors to be sensitive to glycaemic load achieved by varying the form and amount of available and unavailable carbohydrate, suggesting a reduced risk of CHD.

Such risk factor improvement in respect of CHD was generally evident only among those with abnormality in fasting glucose, which is not always evident in studies from authors who have categorised their participants as at risk of CHD.

Healthy people

There is good evidence of no adverse effects on fasting glycaemia (**Fig 30**), fructosamine (**Fig 23**), HbA$_{1c}$ (**Fig 24**), fasting insulin (**Fig 39**), insulin sensitivity (**Fig 41**), B-cell function (retrospective HOMA %B; **Fig 48**), and fasting plasma triglycerides (**Fig 57**). However, these do not imply a lack of physiological responses to the diets in question.

When fasting blood glucose is low, then low glycaemic higher unavailable carbohydrate diets help to keep it up towards the average of normal; healthy people appear among such evidence (**Fig 22**).

Dietary effects of the lower glycaemic higher unavailable carbohydrate diets on fasting blood glucose are similar among those above and below blood glucose levels of 5mmol/L (**Table 27**), though evidence is weak at below 5mmol/L. Healthy people (**Fig 30**) and those at risk of CHD (**Fig 29**) contribute to this effect at below 5mmol/L.

Glycated proteins tend to be reduced by the low glycaemic higher unavailable carbohydrate interventions in people with fasting blood glucose below 5mmol/L (**Fig 38**). Although the evidence for this is weak on the bases of the reviewed studies, similar observations are made elsewhere using fructose.

Insulin sensitivity also may be improved in healthy people consuming the low-glycaemic higher available carbohydrate diets (Fig 41, Table 34). Although the evidence for this is weak, it is consistent with similar but significant evidence from ostensibly healthy non-diabetics (**Table 34**).

Changes in pancreatic function (HOMA %B) in ostensibly healthy non-diabetics and again in healthy people alone move towards a pivotal normal of 100%. Thus when HOMA %B is low (<100%) the intervention diets generally increase this score, which may help protect against the progression to diabetes (**Fig 46** and **Table 41**) in addition to restoring function in type-2 diabetics (**Fig 47**). Such evidence is very weak in healthy people (Table 41), but upheld somewhat by consistency of observations across the different health types, including all health types combined bar diabetics and all health types combined when evidence appear strong (**Table 41**).

Differences in fasting plasma triglyceride concentrations in healthy people may co-vary with differences in glycaemic load of the treatment (**Fig 57**), again however, the evidence is weak and supported only by a similar significant relationship for all studies combined.

Departures in metabolism from central normal values are small in healthy individuals hence it is expected that these physiological responses would be difficult to detect and weak statistically, especially given the small number of studies. The meta-analyses suggest however that when there is strong evidence over all studies combined, the results from healthy people are consistent and supportive of the overall effect of low glycaemic high unavailable carbohydrate diets.

Diabetic complications and coronary events

No study reported on diabetic complications or on coronary events. Reasons for this are likely to be the same as those given below for mortality.

Hypoglycaemic events in type-1 diabetic patients were either unchanged (Lafrance, Rabasa-Lhoret et al. 1998; Gilbertson, Brand-Miller et al. 2001) or halved in numbers (Giacco, Parillo et al. 2000). The low glycaemic diet in the last study was accompanied by a 24 g rise in the amount of unavailable carbohydrate, whereas the first study showed no change (or 2 g decease); Gilberston et al (2001) did not report intakes of unavailable carbohydrate. Data related to 'glyc(a)emic load or index or indices' (prior to 2005) do not allow an assessment of whether the reduced experience of hypoglycaemia is related to lower glycaemic index of available carbohydrate, exchange of available with unavailable carbohydrate or simply just more unavailable carbohydrate.

Mortality

Mortality was not a primary end point of any study retrieved via the literature search performed. No study reported that any participants died related to diabetes, coronary heart disease or other condition. However, studies were too short in duration and too small in participant numbers to yield reliable statistics on mortality. Moreover, many of the studies were small and intensive

due to collection of study data. Studies may have been more attractive to the healthier end of the spectrum of patients.

Duration of treatment

On consuming the lower glycaemic (and sometimes higher unavailable carbohydrate) diets there is a slow reduction of body weight that is more than that seen with the control diet (**Fig 18**). This reduction is progressive up to 1 year after which there is no data in the database (**Fig 20**).

In respect of fasting blood glucose, observations made in studies ≥12 weeks duration appear as predictable as observations made in studies of <12 weeks duration (**Fig 31**), both periods show marked falls in fasting blood glucose in those with well above normal capillary glucose concentrations and small change in those people with capillary glucose close by 5 mmol/L. Observed and model predicted differences in fasting blood glucose at or beyond 12 weeks of treatment are not significantly different (**Fig 31**).

Among type-2 diabetics there is only one study prior to 2005 on fructosamine concentrations in the category ≥12 weeks duration. The effect seen was greater than at <12 weeks duration among other studies (**Fig 34**).

Five studies ≥12 weeks duration in type-2 diabetics yield results for glycated haemoglobin comparable with thirteen studies at <12 weeks duration (**Fig 34**).

Among 4 and 14 studies conducted for ≥12 and < 12 weeks treatment duration respectively, the effect on insulin sensitivity was similar, though evidence was weaker for studies of ≥12 weeks duration (**Fig 43**).

The combined effect of reduction of glycaemic load and intervention (jump), which have opposing influences, indicates no overall effects on fasting triglycerides in 5 and 26 studies at ≥12 and < 12 weeks treatment duration respectively (**Table 46**).

Glycaemic load versus glycaemic index

The present studies were intended ostensibly to investigate diets of reduced glycaemic index at similar levels of available carbohydrate intake. It is clear however that changes in glycaemic load also occur due to a weight for weight exchange of available and unavailable carbohydrate (**Figs 10** and **11**) and reduced intake of available carbohydrate (**Fig 5**). One not surprising consequence is that glycaemic load reduction is better predicted by the glycaemic index of total rather than available carbohydrate (**Fig 9**). Unavailable carbohydrate evidently contributes to influences on physiological and health responses linked to glycaemic load by this mechanism in addition to any direct influence the unavailable carbohydrate may have.

It is important to realise that fat intake is not influence by the variably lower glycaemic, variably higher unavailable carbohydrate, interventions reviewed here. There is some evidence that fat intake may actually fall in the ad libitum studies given above moderate intensity of treatment (**Figs 6** and **14,** and **Tables 4** and **11**). It cannot be argued, therefore, that physiological and heath responses to glycaemic index or load could or would arise due to an energy compensatory mechanism replacing the lower available carbohydrate intake by more dietary fat.

Differences in fat intake may however occur between treatments during intervention studies that are unrelated to changes in glycaemic index (or to exchange of available and unavailable carbohydrate). Such differences may confound interpretation of results as noted below (see section on 'Similarities making a difference').

Difference in glycaemic load has a five-fold stronger relation (P-value) to resulting change in body weight than has glycaemic index. Change in body wt is nevertheless similarly sensitivity to both (**Table 17**, P values differ while differences in regression slopes are due to differing units).

Glycaemic load and index associate with fasting blood glucose with similar strength of evidence (P-values) in these studies (**Tables 25** and **29**), and apparent differences in sensitivity (regression slopes) are again explained by differences in the units of expression (**Table 29**). Glycaemic load has some advantage because the exchange of available and unavailable carbohydrate (**Figs 28** and **29**) increases the capacity to effect change in the glycaemic load experienced.   According to **Fig 28**, a reduction in the effect size for unavailable carbohydrate occurs as it becomes managed as part of the carbohydrate exchange. The sensitivity of fasting blood glucose to these carbohydrate exchanges is similar whether or not the available – unavailable carbohydrate exchange is implemented. This suggests that glycaemic index of available carbohydrate and exchange of available and unavailable carbohydrate have very similar influence on fasting blood glucose, independently of any direct effect unavailable carbohydrate has.

It is also evident (**Figs 23** to **25** and **28**) that unavailable carbohydrate has a second effect. This effect is the one seen to remain associated with unavailable carbohydrate in **Fig 28** after managing the unavailable carbohydrate as a part of the carbohydrate exchange.   Presumably this represents a more direct role to reduce fasting blood glucose. Indeed, the impact of unavailable carbohydrate through these two effects appears to be dominant over modifying the glycaemic response alone via exchange of available carbohydrates. However, both would be needed for optimal control of fasting blood glucose.

Insulin sensitivity also responds favourably to lowering in the quotient for either GI_{AC} or GI_T. The strength of association (P-value) was similar for each expression (**Table 38**). However, glycaemic index does not appear to be a unique index of the change in glycaemic load or indicator of likely improvement in insulin sensitivity (**Table 38**). Including unavailable carbohydrate in the quotients denominator (creating GI_T rather than GI_{AC}) seems to improve the association with insulin sensitivity from a regression slope of 0.89 to 0.92 % per unit GI; this rather than lowering the percentage improvement as would be expected from a simple dilution effect. Including

protein in the quotient's denominator, which may reduce both fat and available carbohydrate intake, leads to greater sensitivity (1.33). Considering fat as if it were pure glucose (both macronutrients elevate protein glycation) by including it in both the numerator and denominator of the quotient increased the sensitivity of association with insulin sensitivity further still (1.67). In communicating glycaemic load reduction it would however be important to avoid scope for attempts to reduce the load by way of elevating fat intake and the last quotient does this (note that fat is considered above as though just as deleterious as pure glucose).

Similarities making a difference

Our earlier discussion of a lack of association between glycaemic index and fat intake should not imply that differences in fat intake between control and treatment arms do not arise in individual studies. Differences in fat intake can occur independently of effort to lower the glycaemic index, and may confound interpretation of study observations. A case in point is the triglyceride response to interventions, which covaries with changes in fat intake (unrelated to glycaemic index or load) confounding the simply meta-analysis (**Fig 56**). After adjustment for fat intake, a change in fasting triglycerides and glycaemic load is evidently dose-dependent (**Fig 55** and **Table 48**).

Although authors intended fat intake to be similar in treatment and control interventions of their studies, the small differences that exists can, evidently, confound interpretation of meta-analyses. This was seen both with meta-analyses on triglycerides (above) and with factors affecting glycaemic load, such as in **Fig 10**.

Thus, author suggestions of similarities can add up to make an appreciable and significant difference in during meta-analysis.

Large bowel awareness

Low glycaemic diets, especially those containing large amounts of unavailable carbohydrate may cause flatulence, meteorisms and diarrhoea. Among the 45 intervention studies with such diets none included such measures of

awareness as primary or secondary outcome measures. Limited information was available from one study, which noted over the course of 24 weeks about a half of the participants recorded more but minor effects on the lower than the higher glycaemic diet and which may be due to ingesting more fermentable carbohydrate (Giacco, Parillo et al. 2000).

Adverse nutritional and metabolic effects

With very small reductions in glycaemic index there is evidence of small rises in available carbohydrate intake (15-35 g/d; **Table 3**), metabolisable energy intake (48 to 1009 kJ/d; **Table 2**), and glycaemic load (8 to 22 g eq. /d; **Table 6**). Linked to rise in glycaemic load is evidence of rise in metabolisable energy (**Table 9**), body weight (**Fig 18**) and triglycerides (**Fig 56**). Such findings indicate improvement may be necessary in the advice we given currently about glycaemic index. Such improvement may be necessary to limit these potentially adverse responses among those people making only minor effort to change their diets. Options for change might include: a) A more direct messages to reduce their glycaemic load and their saturated fat intake. b) To implement glycaemic index of total carbohydrate rather than available carbohydrate. c) To lower glycaemic load by available and unavailable carbohydrate exchanges in addition to lowering the glycaemic index of available carbohydrate, and d) to increase the intake of nonglycaemic and aglycaemic carbohydrate.

THE AUTHORS

Author contributions

The first author (GL) had responsibility for every aspect of this review. GL and RT undertook data collection, GL undertook the analysis and first draft of the report. TH separated the report into the two 'books' and commented on the data. GL undertook to verify the data and its reporting subsequent to the workshop to prepare it for publication

Declarations of interest

GL is a nutritional biochemist, and director of an independent nutrition consultancy. Sponsors of his work are listed at www.inlogic.co.uk. He was commissioned and funded by ILSI Europe for undertaking the work reported herein, for which he commissioned and funded support from RT. RT is a biochemist and molecular geneticist currently funded by grant from the University of Oxford at Merton College. TH is an employee of Kellogg Europe. None of the authors took part in any of the studies analysed.

REFERENCES

Agus, M. S., J. F. Swain, et al. (2000). "Dietary composition and physiologic adaptations to energy restriction." <u>American Journal of Clinical Nutrition</u> **71**(4): 901-7.

Anderson, J. W., K. M. Randles, et al. (2004). "Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence." <u>Journal of the American College of Nutrition</u> **23**(1): 5-17.

Anfinsen, J. R., T. Wolver, et al. (2004). Methods and systems for determining and controlling glycaemic responses. US 0043106 A1.

Ba-Jaber, A. S., A. O. Al-Fouaz, et al. (1998). "Effects of glycaemic index and type of dietary fibers on some biochemical indices of non-insulin dependent diabetes mellitus subjects." <u>Journal of King Saud University, Agricultural Sciences</u> **10**(1): 109-123.

Barkoukis, H., K. M. Fiedler, et al. (2002). "A combined high-fiber, low-glycemic index diet normalizes glucose tolerance and reduces hyperglycemia and hyperinsulinemia in adults with hepatic cirrhosis." <u>J Am Diet Assoc</u> **102**(10): 1503-7; discussion 1507-8.

Bjorck, I. and H. L. Elmstahl (2003). "The glycaemic index: importance of dietary fibre and other food properties." <u>Proc Nutr Soc</u> **62**(1): 201-6.

Bouche, C., S. W. Rizkalla, et al. (2002). "Five-week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight nondiabetic men." <u>Diabetes Care</u> **25**(5): 822-8.

Brand, J. C., S. Colagiuri, et al. (1991). "Low-glycemic index foods improve long-term glycemic control in NIDDM." <u>Diabetes Care</u> **14**(2): 95-101.

Brand-Miller, J. C., P. Petocz, et al. (2003). "Meta-analysis of low-glycemic index diets in the management of diabetes: response to Franz." <u>Diabetes Care</u> **26**(12): 3363-4; author reply 3364-5.

Brennan, C. S. (2005). "Dietary fibre, glycaemic response, and diabetes." <u>Mol Nutr Food Res</u> **49**(6): 560-70.

Brouns, F., I. Bjorck, et al. (2005). "Glycaemic index methodology." <u>Nutrition Research Reviews</u> **18**: 145-171.

Brynes, A. E., C. Mark Edwards, et al. (2003). "A randomised four-intervention crossover study investigating the effect of carbohydrates on daytime profiles of insulin, glucose, non-esterified fatty acids and triacylglycerols in middle-aged men." <u>Br J Nutr</u> **89**(2): 207-18.

Calle-Pascual, A. L., V. Gomez, et al. (1988). "Foods with a low glycemic index do not improve glycemic control of both type-1 and type-2 diabetic patients after one month of therapy." <u>Diabete Metab</u> **14**(5): 629-33.

Carels, R. A., L. A. Darby, et al. (2005). "Education on the glycemic index of foods fails to improve treatment outcomes in a behavioral weight loss program." <u>Eat Behav</u> **6**(2): 145-50.

Chantelau, E., G. E. Sonnenberg, et al. (1985). "Importance of the glycaemic index of foods containing carbohydrate for metabolic control of type-I diabetics having insulin pump treatment." <u>Aktuelle Ernährungsmedizin</u> **10**(6): 236-240.

Clapp, J. F., III (2002). "Maternal carbohydrate intake and pregnancy outcome." <u>Proceedings of the Nutrition Society</u> **61**(1): 45-50.

Colagiuri, S., A. Sandbaek, et al. (2003). "Comparability of venous and capillary glucose measurements in blood." Diabet Med **20**(11): 953-6.

Collier, G. R., S. Giudici, et al. (1988). "Low glycaemic index starchy foods improve glucose control and lower serum cholesterol in diabetic children." Diabetes Nutrition and metabolism **1**(1): 11-19.

Deeks J, Higgins J, et al. (2002). Section 8: Analysis and presentation of results. Cochrane Reviewers' Handbook 4.2.2.

Diaz, E. O., J. E. Galgani, et al. (2004). "Effect of glycemic index on whole-body substrate oxidation in obese women." Int J Obes Relat Metab Disord.

Dumesnil, J. G., J. Turgeon, et al. (2001). "Effect of a low-glycaemic index--low-fat--high protein diet on the atherogenic metabolic risk profile of abdominally obese men." Br J Nutr **86**(5): 557-68.

Ebbeling, C. B., M. M. Leidig, et al. (2003). "A reduced-glycemic load diet in the treatment of adolescent obesity." Archives of Pediatric and Adolescent Medicine **157**(8): 773-9.

FAO (2003). Food energy - methods of analysis and conversion factors. FAO Food and Nutrition Paper No. 77. Rome, Food and Agriculture Organisation.

Fontvieille, A. M., M. Acosta, et al. (1988). "A moderate switch from high to low glycaemic-index foods for three weeks improves the metabolic control of Type-1 (IDDM) diabetic subjects." Diabetes Nutrition and Metabolism **1**: 139-143.

Fontvieille, A. M., S. W. Rizkalla, et al. (1992). "The use of low glycaemic index foods improves metabolic control of diabetic patients over five weeks." Diabet Med **9**(5): 444-50.

Foster-Powell, K., S. H. Holt, et al. (2002). "International table of glycemic index and glycemic load values: 2002." American Journal of Clinical Nutrition **76**(1): 5-56.

Foster-Powell, K. and J. B. Miller (1995). "International tables of glycemic index." American Journal of Clinical Nutrition **62**(4): 871S-890S.

Franceschi, S., L. Dal Maso, et al. (2001). "Dietary glycemic load and colorectal cancer risk." Ann Oncol **12**(2): 173-8.

Frost, G., B. Keogh, et al. (1996). "The effect of low-glycemic carbohydrate on insulin and glucose response in vivo and in vitro in patients with coronary heart disease." Metabolism **45**(6): 669-72.

Frost, G., A. Leeds, et al. (1998). "Insulin sensitivity in women at risk of coronary heart disease and the effect of a low glycemic diet." Metabolism **47**(10): 1245-51.

Frost, G., J. Wilding, et al. (1994). "Dietary advice based on the glycaemic index improves dietary profile and metabolic control in type-2 diabetic patients." Diabet Med **11**(4): 397-401.

Frost, G. S., A. E. Brynes, et al. (2004). "A prospective randomised trial to determine the efficacy of a low glycaemic index diet given in addition to healthy eating and weight loss advice in patients with coronary heart disease." Eur J Clin Nutr **58**(1): 121-7.

Giacco, R., G. Clemente, et al. (2004). "Effects of short-chain fructo-oligosaccharides on glucose and lipid metabolism in mild hypercholesterolaemic individuals." Clinical Nutrition **23**(3): 331-40.

Giacco, R., M. Parillo, et al. (2000). "Long-term dietary treatment with increased amounts of fiber-rich low-glycemic index natural foods improves blood glucose control and reduces the number of hypoglycemic events in type-1 diabetic patients." Diabetes Care **23**(10): 1461-6.

Gilbertson, H. R., J. C. Brand-Miller, et al. (2001). "The effect of flexible low glycemic index dietary advice versus measured carbohydrate exchange diets on glycemic control in children with type-1 diabetes." Diabetes Care **24**(7): 1137-43.

Gilbertson, H. R., A. W. Thorburn, et al. (2003). "Effect of low-glycemic-index dietary advice on dietary quality and food choice in children with type-1 diabetes." Am J Clin Nutr **77**(1): 83-90.

Giovannucci, E. (2001). "Insulin, insulin-like growth factors and colon cancer: a review of the evidence." J Nutr **131**(11 Suppl): 3109S-20S.

Golay, A., B. Koellreutter, et al. (1992). "The effect of muesli or cornflakes at breakfast on carbohydrate metabolism in type-2 diabetic patients." Diabetes Res Clin Pract **15**(2): 135-41.

Haffner, S. M. (2002). "Can reducing peaks prevent type-2 diabetes: implication from recent diabetes prevention trials." Int J Clin Pract Suppl(129): 33-9.

Harbis, A., S. Perdreau, et al. (2004). "Glycemic and insulinemic meal responses modulate postprandial hepatic and intestinal lipoprotein accumulation in obese, insulin-resistant subjects." Am J Clin Nutr **80**(4): 896-902.

Heilbronn, L. K., M. Noakes, et al. (2002). "The effect of high- and low-glycemic index energy restricted diets on plasma lipid and glucose profiles in type-2 diabetic subjects with varying glycemic control." J Am Coll Nutr **21**(2): 120-7.

Herrmann, T. S., M. L. Bean, et al. (2001). "High glycemic index carbohydrate diet alters the diurnal rhythm of leptin but not insulin concentrations." Exp Biol Med (Maywood) **226**(11): 1037-44.

Hofman, Z., J. D. van Drunen, et al. (2004). "The effect of different nutritional feeds on the postprandial glucose response in healthy volunteers and patients with type-2 diabetes." Eur J Clin Nutr **58**(11): 1553-6.

Jarvi, A. E., B. E. Karlstrom, et al. (1999). "Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type-2 diabetic patients." Diabetes Care **22**(1): 10-8.

Jenkins, D. J., M. Axelsen, et al. (2000). "Dietary fibre, lente carbohydrates and the insulin-resistant diseases." Br J Nutr **83 Suppl 1**: S157-63.

Jenkins, D. J., T. M. Wolever, et al. (1988). "Low-glycemic-index starchy foods in the diabetic diet." Am J Clin Nutr **48**(2): 248-54.

Jenkins, D. J., T. M. Wolever, et al. (1987a). "Metabolic effects of a low-glycemic-index diet." Am J Clin Nutr **46**(6): 968-75.

Jenkins, D. J., T. M. Wolever, et al. (1985). "Low glycemic index carbohydrate foods in the management of hyperlipidemia." Am J Clin Nutr **42**(4): 604-17.

Jenkins, D. J., T. M. Wolever, et al. (1987b). "Low-glycemic index diet in hyperlipidemia: use of traditional starchy foods." Am J Clin Nutr **46**(1): 66-71.

Jenkins, D. J., T. M. Wolever, et al. (1981). "Glycemic index of foods: a physiological basis for carbohydrate exchange." American Journal of Clinical Nutrition **34**(3): 362-6.

Jimenez-Cruz, A., M. Bacardi-Gascon, et al. (2003). "A flexible, low-glycemic index mexican-style diet in overweight and obese subjects with type-2 diabetes improves metabolic parameters during a 6-week treatment period." Diabetes Care **26**(7): 1967-70.

Jiménez-Cruz, A., W. H. Turnbull, et al. (2004). "A high-fiber, moderate-glycemic-index, Mexican style diet improves dyslipidemia in individuals with type-2 diabetes." Nutrition Research **24**(1): 19-27.

Kabir, M., J. M. Oppert, et al. (2002). "Four-week low-glycemic index breakfast with a modest amount of soluble fibers in type-2 diabetic men." Metabolism **51**(7): 819-26.

Kelly, S., G. Frost, et al. (2004). "Low glycaemic index diets for coronary heart disease." Cochrane Database Syst Rev(4): CD004467.

Kiens, B. and E. A. Richter (1996). "Types of carbohydrate in an ordinary diet affect insulin action and muscle substrates in humans." Am J Clin Nutr **63**(1): 47-53.

Komindr, S., S. Ingsriswang, et al. (2001). "Effect of long-term intake of Asian food with different glycemic indices on diabetic control and protein conservation in type-2 diabetic patients." J Med Assoc Thai **84**(1): 85-97.

Kurup, P. G. and S. Krishnamurthy (1993). "Glycemic response and lipemic index of rice, raggi and tapioca as compared to wheat diet in human." Indian J Exp Biol **31**(3): 291-3.

Lafrance, L., R. Rabasa-Lhoret, et al. (1998). "Effects of different glycaemic index foods and dietary fibre intake on glycaemic control in type-1 diabetic patients on intensive insulin therapy." Diabet Med **15**(11): 972-8.

Liu, S., W. C. Willett, et al. (2000). "A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women." American Journal of Clinical Nutrition **71**(6): 1455-61.

Livesey, G. (1990). "Energy values of unavailable carbohydrate and diets: an inquiry and analysis." American Journal of Clinical Nutrition **51**(4): 617-37.

Livesey, G. (2003). "Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties." Nutrition Research Reviews **16**: 163-191.

Livesey, G. (2005). Non-digestible carbohydrates and glycaemic control. Nutrition Safari for Inovative Solutions, Proceedings of the 18th International Congress of Nutrition. H. Vorster, R. Blaauw, M. Dhansayet al. Durban SA, ICC.

Livesey, G. (2005a). "Low-glycaemic diets and health - implications for obesity." Proc Nutr Soc **161**: 105-113.

Livesey, G. (2005b). Non-digestible carbohydrates and glycaemic control. Nutrition Safari for Inovative Solutions, Proceedings of the 18th International Congress of Nutrition. H. Vorster, R. Blaauw, M. Dhansayet al. Durban SA, ICC.

Livesey, G. (2006). Glycaemic responses and toleration. Sweeteners and sugar alternatives in food technology. H. Mitchell. Oxford, UK, Blackwell: 000 - 000.

Lorenzo, A. d., M. L. Petroni, et al. (2001). "Use of quality control indices in moderately hypocaloric Mediterranean diet for treatment of obesity." Diabetes, Nutrition & Metabolism 14(4): 181-188.

Luscombe, N. D., M. Noakes, et al. (1999). "Diets high and low in glycemic index versus high monounsaturated fat diets: effects on glucose and lipid metabolism in NIDDM." Eur J Clin Nutr 53(6): 473-8.

McCance, R. A. and R. D. Lawrence (1929). The carbohydrate content of foods. Medical Research Council Special Report Series No 135. London, Her Majesty's Stationery Office.

Minehira, K. and L. Tappy (2002). "Dietary and lifestyle interventions in the management of the metabolic syndrome: present status and future perspective." Eur J Clin Nutr 56(12): 7 p following 1262.

Monro, J. (2003). "Redefining the glycemic index for dietary management of postprandial glycemia." Journal of Nutrition 133(12): 4256-8.

Morales, L. M., M. Semprun-Fereira, et al. (1997). "Improved triglyceride control with low glycaemic index-high carbohydrate modified-lipid diet in a hypertriglyceridaemic child." Acta Paediatr 86(7): 772-4.

Oh, K., F. B. Hu, et al. (2005). "Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women." American Journal of Epidemiology 161(2): 161-9.

Opperman, A. M., C. S. Venter, et al. (2004). "Meta-analysis of the health effects of using the glycaemic index in meal-planning." British Journal of Nutrition 92(3): 367-81.

Ostman, E. M., A. H. Frid, et al. (2006). "A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance." Eur J Clin Nutr 60(3): 334-41.

Pawlak, D. B., C. B. Ebbeling, et al. (2002). "Should obese patients be counselled to follow a low-glycaemic index diet? Yes." Obesity Reviews 3(4): 235-43.

Pekka, P., P. Pirjo, et al. (2002). "Influencing public nutrition for non-communicable disease prevention: from community intervention to national programme--experiences from Finland." Public Health Nutr 5(1A): 245-51.

Pereira, M. A., J. Swain, et al. (2004). "Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss." Jama 292(20): 2482-90.

Puska, P. (2002). "Nutrition and global prevention on non-communicable diseases." Asia Pac J Clin Nutr 11 Suppl 9: S755-8.

Raben, A. (2002). "Should obese patients be counselled to follow a low-glycaemic index diet? No." Obesity Reviews 3(4): 245-56.

Rickard, K. A., J. L. Cleveland, et al. (2001). "Similar glycemic responses to high versus moderate sucrose-containing foods in test meals for adolescents with type-1 diabetes and fasting euglycemia." Journal of the American Dietetic Association 101(10): 1202-1205.

Ritz, P., M. Krempf, et al. (1991). "Comparative continuous-indirect-calorimetry study of two carbohydrates with different glycemic indices." Am J Clin Nutr **54**(5): 855-9.

Rizkalla, S. W., L. Taghrid, et al. (2004). "Improved plasma glucose control, whole-body glucose utilization, and lipid profile on a low-glycemic index diet in type-2 diabetic men: a randomized controlled trial." Diabetes Care **27**(8): 1866-72.

Robertson, M. D., A. S. Bickerton, et al. (2005). "Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism." Am J Clin Nutr **82**(3): 559-67.

Robertson, M. D., J. M. Currie, et al. (2003). "Prior short-term consumption of resistant starch enhances postprandial insulin sensitivity in healthy subjects." Diabetologia **46**(5): 659-65.

Robertson, M. D., G. Livesey, et al. (2000). "Evidence for altered control of glucose disposal after total colectomy." British Journal of Nutrition **84**(6): 813-9.

Robertson, M. D., G. Livesey, et al. (1999). "The influence of the colon on postprandial glucagon-like peptide 1 (7-36) amide concentration in man." Journal of Endocrinology **161**(1): 25-31.

Rowlet, R. (2005). A Dictionary of Units of Measurement. Chapel Hill, NC, Center for Mathematics and Science Education, University of North Carolina at Chapel Hill.**:** http://www.unc.edu/~rowlett/units/scales/clinical_data.html, retrieved 27 April 2006.

Salmeron, J., A. Ascherio, et al. (1997). "Dietary fiber, glycemic load, and risk of NIDDM in men." Diabetes Care **20**(4): 545-50.

Santacroce, G., G. Forlani, et al. (1990). "Long-term effects of eating sucrose on metabolic control of type-1 (insulin-dependent) diabetic outpatients." Acta Diabetol Lat **27**(4): 365-70.

Schafer, G., U. Schenk, et al. (2003). "Comparison of the effects of dried peas with those of potatoes in mixed meals on postprandial glucose and insulin concentrations in patients with type-2 diabetes." Am J Clin Nutr **78**(1): 99-103.

Slabber, M., H. C. Barnard, et al. (1994). "Effects of a low-insulin-response, energy-restricted diet on weight loss and plasma insulin concentrations in hyperinsulinemic obese females." American Journal of Clinical Nurition **60**(1): 48-53.

Sloth, B., I. Krog-Mikkelsen, et al. (2004). "No difference in body weight decrease between a low-glycemic-index and a high-glycemic-index diet but reduced LDL cholesterol after 10-wk ad libitum intake of the low-glycemic-index diet." American Journal of Clinical Nurition **80**(2): 337-347.

Spieth, L. E., J. D. Harnish, et al. (2000). "A low-glycemic index diet in the treatment of pediatric obesity." Archives of Pediatric and Adolescent Medicine **154**(9): 947-51.

Thorburn, A. W., P. A. Crapo, et al. (1990). "Long-term effects of dietary fructose on carbohydrate metabolism in non-insulin-dependent diabetes mellitus." Metabolism **39**(1): 58-63.

Tsihlias, E. B., A. L. Gibbs, et al. (2000). "Comparison of high- and low-glycemic-index breakfast cereals with monounsaturated fat in the long-

term dietary management of type-2 diabetes." Am J Clin Nutr **72**(2): 439-49.

Turtle, J. R. (2000). "The economic burden of insulin resistance." Int J Clin Pract Suppl(113): 23-8.

Wallace, T. M., J. C. Levy, et al. (2004). "Use and abuse of HOMA modeling." Diabetes Care **27**(6): 1487-95.

Wallace, T. M. and D. R. Matthews (2002). "Coefficient of failure: a methodology for examining longitudinal beta-cell function in Type-2 diabetes." Diabetes Medicine **19**(6): 465-9.

WHO/FAO (1998). Carbohydrates in human nutrition. FAO Food and Nutrition Paper No 66. Rome, Food and Agriculture Organisation.

WHO/FAO (2003). Diet, nutrition and the prevention of chronic diseases. Report of a Joint WHO/FAO Expert Consultation. WHO Technical Report Series 916. Geneva, World Health Organisation.

Wolever, T. M., D. J. Jenkins, et al. (1992b). "Beneficial effect of a low glycaemic index diet in type-2 diabetes." Diabet Med **9**(5): 451-8.

Wolever, T. M., D. J. Jenkins, et al. (1992a). "Beneficial effect of low-glycemic index diet in overweight NIDDM subjects." Diabetes Care **15**(4): 562-4.

Wolever, T. M. and C. Mehling (2002). "High-carbohydrate-low-glycaemic index dietary advice improves glucose disposition index in subjects with impaired glucose tolerance." British Journal of Nutrition **87**(5): 477-87.

Wolever, T. M. and C. Mehling (2002). "High-carbohydrate-low-glycaemic index dietary advice improves glucose disposition index in subjects with impaired glucose tolerance." Br J Nutr **87**(5): 477-87.

Wolever, T. M. and C. Mehling (2003). "Long-term effect of varying the source or amount of dietary carbohydrate on postprandial plasma glucose, insulin, triacylglycerol, and free fatty acid concentrations in subjects with impaired glucose tolerance." Am J Clin Nutr **77**(3): 612-21.

YinFa, Z., Y. YueXin, et al. (2003). "The research on application in the education with glycemic index in diabetic patients." Acta Nutrimenta Sinica **25**(3): 248-252.