
Article:
Evans, CEL orcid.org/0000-0002-4065-4397, Greenwood, DC orcid.org/0000-0001-7035-3096, Threapleton, DE et al. (3 more authors) (2017) Glycemic index, glycemic load, and blood pressure: a systematic review and meta-analysis of randomized controlled trials. American Journal of Clinical Nutrition, 105 (5). pp. 1176-1190. ISSN 0002-9165

https://doi.org/10.3945/ajcn.116.143685

Glycemic index, glycemic load and blood pressure: A systematic review and meta-analysis of RCTs.

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Sources of support:

The large systematic review of carbohydrates and cardio-metabolic health was funded by the Department of Health (DH) for England. The DH were involved in the design of the protocol.

Short running head:

Glycemic Index and blood pressure

Key words: Glycemic index, glycemic load, systematic review, blood pressure, diet

Abbreviations:

BMI – body mass index

CI – confidence interval

CVD – cardiovascular disease

DBP - diastolic blood pressure

DH – Department of Health

GI – Glycemic Index

GL – Glycemic Load

RCT – randomized controlled trial

SBP - systolic blood pressure

Abstract

Background: High blood pressure is a strong risk factor for cardiovascular disease.

Objectives: The aim was to determine the associations of dietary glycemic index (GI) and glycemic load (GL) with systolic blood pressure (SBP) and diastolic blood pressure (DBP) in healthy individuals.

Design: A systematic review and meta-analysis of randomized controlled trials (RCTs) was carried out. Databases were searched for eligible RCTs in two phases. Medline, Embase, CAB Abstracts, BIOSIS, ISI Web of Science and the Cochrane Library were searched from January 1990 to December 2009. An updated search was undertaken using Medline and Embase from January 2010 to September 2016. Trials were included if they reported author-defined high and low GI or GL diets and blood pressure, were of at least 6 weeks duration, and comprised healthy participants without chronic conditions. Data were extracted and analyzed using STATA statistical software. Pooled estimates and 95% confidence intervals (CI) were calculated using weighted mean differences and random effects models.

Results: Data were extracted from 14 trials comprising 1097 participants. Thirteen trials provided information on differences in GI between control and intervention arms. A median reduction in GI of 10 units, reduced the overall pooled estimates for SBP and DBP by 1.1mmHg (95% CI, -0.3 to 2.5, p=0.11) and 1.3 mmHg (95% CI 0.2 to 2.3, p=0.02) respectively. Nine trials reported information on differences in GL between arms. A median reduction in GL of 28 units reduced the overall pooled estimates for SBP and DBP by 2.0 mmHg (95% CI, 0.2 to 3.8, p=0.03) and 1.4 mmHg (95% CI, 0.1 to 2.6, p=0.03) respectively.

Conclusion: This review of healthy individuals, indicated that a lower glycemic diet may lead to important reductions in blood pressure. However, many of the trials included in the analysis reported important sources of bias.

PROSPERO registration number:CRD42016049026

Introduction

A third of all deaths in the US(1) and the UK(2) and nearly half of all deaths across Europe(3) are attributed to diseases of the heart and circulatory system. Established markers of cardiovascular disease (CVD) risk include systolic and diastolic blood pressure. Blood pressure together with total, LDL and HDL cholesterol and BMI are included in predictive tools measuring risk of mortality over 10 years (2). A third of healthy adult populations are estimated to have blood pressure values outside the desirable range(1, 4). This is an important public health and primary care concern as it is estimated that each 2 mmHg reduction in systolic blood pressure (SBP) and 1mmHg reduction in diastolic blood pressure (DBP) is associated with a 10% reduction in the risk of CVD(5).

A review of trials investigating the effect of dietary advice on markers of CVD concluded that reductions in dietary fat and increases in dietary fiber intake are associated with improvements in SBP and DBP(6). Research to date has mainly focused on individual major nutrients such as fat and fiber, however dietary patterns are increasingly highlighted as important for health(7). Results from the INTERHEART study using data from 52 countries concluded that an unhealthy dietary pattern accounts for approximately 30% of the risk of acute myocardial infarction(8) and there is ample evidence for an association between a Mediterranean diet and impaired cardiovascular health(9, 10).

Evidence is emerging that a low glycemic index (GI) diet; a dietary pattern characterized by foods lower in refined starches and sugars and higher in dietary fiber, particularly soluble fiber, and may be associated with better health outcomes; including better glucose control and lipid profile(11-13). Unlike Mediterranean type diets, low GI diets are not limited by intake of specific regional foods and therefore may be more flexible and appropriate in different settings. Diets that have a large number of foods with GI values below 55 (compared with 100 for glucose) are usually considered low GI whereas diets that include many foods with values above

70 are considered high GI diets(14). Similarly, the glycemic load (GL) is the product of a specific food's GI and carbohydrate content(15), thereby taking into account both the quality and quantity of carbohydrate consumed and is usually measured in grams. This may be interpreted as a measure of diet-induced insulin demand(16).

To date, there is conflicting evidence for a link between GI, GL and CVD risk. Higher GI diets increase fasting blood glucose and glycated proteins(13) however, a review in 2004 found no strong evidence that low GI diets reduce the risk of CVD(17). Concerning GL and CVD risk, individual studies suggest that a lower GL diet reduces markers of CVD risk(18, 19). Previous research has focused more on patients with diabetes and individuals with high blood pressure or abnormal blood lipid profiles(20, 21). There is currently no published systematic review and meta-analysis of the associations between GI and GL on blood pressure in healthy populations and a review of the evidence is warranted. Our aim was to undertake a systematic review and meta-analysis to determine the impact of differences in dietary GI or lower GL on SBP and DBP amongst healthy individuals.

Methods

Selection of trials

This review is part of a large review of carbohydrates and cardio-metabolic disease. The protocol is available from the DoH for England(22) and this section of the review is registered with PROSPERO. We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines throughout the review(23). We included parallel or crossover randomized controlled trials (RCTs) in adult participants where they reported a difference in GI, GL, GI diet or GI foods between an intervention group and a comparator group. This difference was 'author defined' in that we did not use our own pre-defined criteria for what constituted a 'higher' or 'lower' GI/GL diet and, therefore, accepted definitions presented within each article. Studies of blood pressure were at least 6 weeks in duration. We excluded studies if ill health or

history of disease was part of the inclusion criteria for the study and where more than 50% of participants had chronic diseases such as hypertension or diabetes or where the study population mean blood pressure exceeded 140/90 and results for non-hypertensive participants were not separately presented. However, we included studies where participants were recruited with risk of metabolic syndrome. Outcomes in the full review but not reported here included additional markers of CVD and inflammation. These can be found on the UK DoH government website and in the protocol(22). No ethics approval was needed as the review consisted of secondary data analysis.

The review was conducted in two phases. We carried out the first phase (as part of the large DoH review) to identify relevant studies published in English from 1990 until December 2009. The following electronic databases were searched: Medline, Pre-Medline (MEDLINE in process), Embase, CAB Abstracts, BIOSIS, ISI Web of Science and The Cochrane Library. Electronic searches were supplemented with hand searches in key journals and citation lists of selected review articles. Search terms included MeSH terms for glycemic index and glycemic load and blood pressure. The BMJ search strategy for trials was used(24). The protocol was agreed by all research personnel prior to starting the review and peer-reviewed by panel members of the Scientific Advisory Committee on Nutrition (SACN) carbohydrate working group and DoH personnel. We carried out an updated search in phase two to identify relevant studies reporting blood pressure with low and high GI/GL diets from January 2010 to September 2016 in Medline and Embase only. We used the same search criteria in phase 2 as in phase 1.

Data screening and extraction

For each reference, we screened article titles and/or abstracts for relevancy once, using the agreed guidelines established at the start of the review. References that were clearly unrelated to the scope of the review and non-peer reviewed research articles such as letters and editorials were marked as ‘not relevant’. All other articles were marked as ‘potentially relevant’ and

moved to another database for the next stage of the process. Full text copies of all 'potentially relevant' papers were reviewed independently by two members of the review team (DT, CC, CE, CN, CW) using an agreed inclusion/exclusion form. Where any disagreement occurred, a third member of the team (VB) arbitrated in the decision.

Data on exposures, outcomes, sample size, participants, study-design and length of intervention, were entered directly into a Microsoft Access database designed by the Nutrition Epidemiology Group at the University of Leeds. Data extraction was completed by one of several members of the review team with serial review for extraction errors. Any anomalies were then checked against the original papers as necessary.

Quality assessment of trials

We assessed the quality of included RCTs using the Cochrane indicators of bias(25). This was undertaken by one reviewer and covered the following issues: sequence generation criteria for random allocation, allocation concealment, blinding of participants, blinding of personnel and outcome assessors, incomplete reporting of outcome data, selective outcome reporting and other potential threats to validity. The results were checked by an additional member of the team (as previously listed) and any disagreements discussed with a third member of the team (VB).

Based on each of the above criteria, we categorized each paper as containing bias, no bias or being unclear. Assessor blinding for individual outcomes was also captured in addition to overall blinding within the trial but only the overall result is provided here. We also determined whether measurement of blood pressure was the primary outcome and assessed the level of adherence to the diet as informative measures of study quality.

Statistical analysis

We extracted data from all arms of the trial and the two arms with the largest difference in GI or GL were included in our analysis. We included results of the trial if data were provided in one

of the following two formats: a difference in blood pressure between the intervention and control group either adjusted or unadjusted for baseline results or a change in blood pressure from baseline to follow up for each arm. For the latter, we calculated the difference in the change between groups using the appropriate t-test to provide the difference between groups along with a measure of variation. If only a p value was provided for the difference between arms or if the results were displayed in a figure but not presented in a table the standard error of the difference between arms was estimated.

We used a random effects meta-analysis of the intervention trial data as our primary outcome. We carried out a fixed effects meta-analysis as a sensitivity analysis. A weighted mean difference was calculated (weighted by the inverse of the variance). Heterogeneity was presented as the proportion of the total variation in study estimates that was due to between study heterogeneity (I^2)(26). It is common to interpret I^2 as being excessive where the value is in excess of 50 to 75%. We chose to use 75% as our cut off as there is higher methodological variability when the exposure is a dietary factor(27). We generated the pooled estimate together with 95% confidence interval (95%CI) but where I^2 values were above 75%, no pooled estimate was generated. We assessed small study effects, such as publication bias, using a funnel plot if the number of studies exceeded ten. A broadly symmetrical funnel plot was taken to indicate an absence of small study effects.

In order to determine whether some heterogeneity was due to existing confounders such as age, weight loss, BMI at baseline, energy or macronutrient intake, we carried out meta-regressions on available data. To determine whether there was a dose response for the association of GI on blood pressure we converted GI difference between groups to the glucose scale (if on the white bread scale) using the methods by Wolever et al.(28) and split the trials at the median into two groups, those with a high difference in GI and those with a low difference in GI to provide the pooled estimate for each sub-group.

Results

Trial characteristics

Fourteen trials comprising 1097 participants provided data on the effects of high or low GI/GL diets on blood pressure, all of which were included in a meta-analysis. The main reasons for exclusion at the second data extraction stage in the original review were related to study design (n=411), type of carbohydrate (n=322), length of the trial (n=265) and lack of healthiness of participants (n=138). A comprehensive list of exclusions is available in the DoH report(22). Eight trials were included in the original search. In the updated search, 482 studies were obtained using the same search criteria, of which 29 were identified as potentially relevant. The reasons for excluding potentially relevant papers were blood pressure not reported at both baseline and follow up (n=6), participants not healthy (n=5), not a relevant GI or GL diet (n=5), not a trial (n=2), less than 6 weeks duration (n=1), not adults (n=2), conference abstract (n=1) and results reported in another paper (n=1) leaving 6 relevant papers in the updated search (figure 1).

The studies were carried out in a number of different countries and therefore a range of populations with different diets were represented (table 1); Nearly half of the studies were conducted in the US (6 studies) and other countries included in the review were the UK (2), Denmark (1), France (1) Germany (1), Italy (1), New Zealand (1) and Spain (1). All the trials used a parallel group design which ranged in duration from 2 to 12 months. The first results reported after the end of the intervention were used in the analyses. All the studies included generally healthy populations, however, most studies included overweight or obese participants, often as part of the inclusion criteria (table 1).

The studies used different methods to achieve low GI or GL diets with some using a whole diet approach and some providing key foods to substitute. See table 1 for intervention details. Estimates of GI and GL ranged from an average GI of 40-54 for the lower GI groups and 53-86

for the higher GI groups and an average GL of approximately 50g/1000kcal for lower GL groups compared with 75-120g/1000kcal for the higher GL groups (see table 1). Two studies reported GI in % but these were not transformed(29, 30). The median difference in GI within each study was 10 units while the median difference in GL was 34 units. One study described the foods consumed by the two groups but did not supply a GI or GL value(31). One study had 3 arms which included a control, low GI and low energy dense diet. The control and low GI diet were compared(32). The glycemic response is determined not only by the nature of the carbohydrate component of a food or diet, but also by the types and amounts of protein, fat and dietary fiber, as well as food processing and storage(33). The information for each study detailed in table 1 indicates that many of the studies were balanced in terms of energy and macronutrients for each group although four of the studies had total carbohydrate contents differing by more than 5% of total energy(18, 19, 34, 35). For the 10 studies that reported actual nutrients (not targets) the median differences in energy, protein, total fat, carbohydrate and fiber between groups were as follows. Median energy was 12 Kcals higher in the low GI diets; the median difference in protein was 1% of total energy lower in the low GI diets; the median difference in total fat was the same; the median difference in carbohydrate was 1.5% total energy higher in the low GI diets and median difference in fiber was 2g lower in the low GI diets.

All studies used adults as participants, who had an average age of between 28 and 54 years. Most studies included men and women as participants although often not in equal numbers. Two studies included only women (31, 36) and one study only men(35). The median number of participants in each trial was 47, with two larger trials reporting results from more than 100 subjects(29, 30).

All studies reported body weight, either in kilograms (kg) or percent weight change at follow up compared with baseline. Body weight decreased in the majority of trials in both groups (see table 1), although weight loss was slightly more pronounced in the low GI diets with a median

difference in weight loss of 0.5kg between groups. The difference between groups was not statistically significant for the majority of studies although the study by Abete(37) reported significant differences between groups with higher weight loss on the low GI diet. Of the 10 studies that reported mean baseline BMI, subjects were mostly overweight or obese men and women following a hypo-energetic diet (generally in the region of 1500kcal/day).

Quality of trials

The results of the quality check are reported in table 2. The majority of the trials reported that subjects and researchers were not blinded to the nature of the intervention, although one study was double blind(36). Ten of the studies stated that there was no blinding of participants(19, 29, 30, 32, 35, 38-41) or both researchers and participants(31). Some trials did not provide sufficient information, particularly on blinding of researchers. Furthermore, only one trial clearly described good allocation concealment(39) while the remaining trials did not provide enough information to make a definite decision. In addition, none of the trials measured blood pressure as the primary outcome. In all studies the primary outcome was a measure of body fatness. Nevertheless, some studies stated that a protocol was followed for measuring blood pressure(29, 31) or provided details on length of time participants were at rest before measurement(18, 19, 32, 35, 37, 39) while the remaining studies did not provide any information. A further indicator of trial quality was the degree to which adherence to the diet was monitored and encouraged. One study used urinary Nitrogen to measure adherence (29) and two studies provided food and checked adherence through food diaries(18, 36). The most common method of assessment was through diaries(31, 33, 34, 38, 39, 42). The remaining trials did not provide any information on adherence. The quality of the studies was, therefore, generally poor with most studies categorized as prone to bias or unclear. This is a common problem with dietary studies due to the difficulties inherent in the conduct of double blind dietary studies. For this reason, we did not exclude studies from the review based on our quality check.

Blood pressure

All 14 studies provided information on, or permitted estimation of, differences in both SBP and DBP between low and high GI diets. Two studies reported data from four arms; Fava et al. included results on differences between low and high GI diets from participants on high carbohydrate and high monounsaturated diets(40) and Gogebakan et al. included results on differences from participants on a low protein and high protein diet(29). The total number of data points possible in the Forest plots was therefore sixteen. Thirteen out of the 14 trials reported the difference in GI between groups in GI units, however one trial did not report this information(31). Nine of the trials reported the difference in GL between groups and eight of these nine trials report that the low GI diet was also the low GL diet. However one study reported that the high GI diet was lower in GL(32).

The summary estimate for all 14 trials (16 comparisons) using random effects methods indicated that SBP was 1.13mmHg (95% CI, -0.25 to 2.51, p=0.11) lower with consumption of a lower GI diet (figure 2). The results for fixed effects methods indicated that SBP was 1.10mmHg (95% CI, -0.20 to 2.40, p=0.10) lower with consumption of a lower GI diet. The estimates for individual studies ranged from -4.9 to 16.0mmHg. The proportion of variation due to real effects rather than sampling error was low (I^2= 9%). The summary estimate for all 14 trials (16 comparisons) using random effects methods indicated that DBP was 1.26mmHg (95% CI, 0.22 to 2.30, p=0.02) lower with consumption of a lower GI diet (figure 3). The results for fixed effect methods indicated that DBP was 1.18mmHg (95% CI, 0.29 to 2.08, p=0.01) lower with consumption of a lower GI diet. The estimates for individual studies ranged from -2.9 to 12.6. The proportion of variation due to real effects rather than sampling error was low (I^2 = 20%). There was no strong evidence of small study bias (figures 4 and 5).

We did not find strong evidence of a dose response either using meta-regression of differences in GI between arms or by splitting trials at the median (10 units) to compare low and high differences in GI between arms (table 3).

We found similar results when we investigated the effects on blood pressure for the nine trials that reported differences in GL (median of 28). For SBP, using random effects methods the summary estimate was 1.98mmHg (95%CI 0.20 to 3.75, p=0.03) and using fixed effects methods the summary estimate was the same (figure 6). For DBP, using random effects methods the summary estimate was 1.35mmHg (95% CI 0.12 to 2.59, p=0.03) and using fixed effects methods the summary estimate was the same (figure 7).

Additional factors affecting blood pressure and glycemic index

In most of the reviewed studies, participants lost weight in both trial arms. Given that weight loss is a driver for reductions in blood pressure and increasing age is a strong causal factor for higher blood pressure (BP), we undertook a meta regression to determine whether differences in blood pressure were due to differences in changes in body weight between arms. We found that for each extra 1 kg in weight loss in the low GI group, SBP reduced by 0.05 mmHg (95% CI -2.01 to 1.92, p=0.96) and DBP reduced by 0.22 mmHg (95% CI -1.40 to 1.84, p=0.78). We also looked at differences in age between studies. For a 10-year increase in age SBP increased by 0.4 mmHg (95% CI -1.3 to 2.1, p=0.65) and DBP increased by 0.3 mmHg (95% CI -1.9 to 2.6, p=0.75). These results indicate that the differences in blood pressure mainly related to GI/GL and were unlikely to be due to major differences in weight loss or age (table 3). Meta-regressions investigating effects of energy and macronutrients on blood pressure outcomes were not significant (see table 3). Furthermore, studies where adherence monitoring was reported were not substantially different from studies where adherence was not reported (table 3).

Discussion

It is established that low GI diets improve glycemic control in people with diabetes or pre-diabetes(12, 13) and reduce lipids in hyperlipidemic individuals(12), however the impact on healthy individuals is in need of clarification. In this first systematic review and meta-analysis of healthy individuals, GI and GL were significantly associated with lower DBP but results were inconsistent for SBP. There was a significant reduction in SBP for low GL diets but a non-significant trend with lower GI diets. Despite these findings, there was no clear dose response and furthermore, sources of bias were evident for the majority of trials included.

High blood pressure is cited as the number one cause of poor health in the largest review of the Global Burden of Disease(43) and is reported to be the main cause of more than half of CVD incidence, including stroke, in the developed world(44). The lower DBP level of 1.4mmHg observed in lower GI/GL diets compared to higher GI/GL diets is smaller than the effect of a low salt diet in a non-hypertensive population as reported in a large review by He et al.(44). However, low GI diets may still have the potential to reduce blood pressure comparable to a moderate decrease in salt intake and potentially to reduce CVD risk by approximately 5%(44). A lower GI diet can be achieved with an increase in pulses, beans, vegetables, whole fruits and high fiber products and lower intakes of sweetened drinks and may therefore offer potential health benefits over and above a high soluble fiber diet alone.

Many of the studies included in this review comprised of overweight participants on energy restricted diets resulting in weight loss in both arms of the trial. Weight is strongly associated with blood pressure, and published reviews have reported that 1Kg of weight loss leads to approximately 1mmHg reduction in SBP and DBP(45, 46). Therefore, even small non-statistically significant differences in weight loss between arms could explain some of the difference in blood pressure between low and high GI/GL diets. However, when we undertook a meta-regression, the extent of weight loss was similar between arms and so it was unlikely that

differences in weight loss explain the differences in blood pressure between high and low GI diets.

Mechanisms

The mechanisms for the effect of low GI diets on blood lipids profiles and blood pressure readings are not clear. A low GI diet is usually high in some types of dietary fiber, in particular soluble fiber but not necessarily low in carbohydrate whereas a low GL diet is low in total carbohydrate. Low GI and GL diets both tend to have a low energy density and this may promote energy intake regulation often leading to weight loss. Weight loss has been identified as a strong predictor of lower blood pressure and therefore is a probable confounder. However, as noted above, the authors think this is unlikely to be the cause in this review as most of the trials were comparing a low energy, low GI or GL diet with a low energy diet of higher GI or GL. Additionally, the trials reported similar differences in body weight between baseline and follow up between the control and intervention groups. In most cases participants in both groups lost similar amounts of weight but in trials of short duration we may be unable to detect weight loss differences that would emerge long term.

Given that changes to blood pressure are a composite of altered sympathovagal balance, leading to increases in heart rate and stroke volume, accompanied by changes to arteriolar tone the impact of high GI diets on both sympathetic tone and endothelial function should be considered. The decrease in blood pressure may be a consequence of lower sugars acting on sympathetic tone and epithelial function rather than just a function of slowly digested starch. Indeed, diets high in fructose are associated with elevated blood pressure(47) and increases in sympathetic tone(48), whilst increased glucose intake is also associated with increases in basal heart rate(49). Furthermore, high plasma uric acid concentrations, associated with both increased fructose and glucose consumption are also associated with endothelial dysfunction(50, 51). Dietary protein has also been shown to have an impact on blood pressure(52). It is not clear to what extent the

improvements in blood pressure are due to individual components of a low GI diet including lower levels of overall carbohydrates and sugars and higher levels of plant proteins and soluble fibers.

Strengths and limitations of this review

This is the first comprehensive review of the effects of GI and GL on blood pressure. It included RCTs, which are considered the highest quality of study, of at least 6 weeks in duration and meta-analysis. The review was carried out using PRISMA guidelines using an established and published protocol.

However, many of the trials included low numbers of participants in each group, far below the sample of many hundreds of participants needed to detect differences in blood pressure of 2mmHg with reasonable power. This resulted in large standard errors for most of the individual estimates and although the values for I^2 were low there was still a wide range of estimates with overlapping confidence intervals indicating high levels of heterogeneity. Limitations of using I^2 as a measure of heterogeneity are discussed in detail by Borenstein et al.(53). Blood pressure was not the primary outcome for any of the trials and therefore the quality of the data on blood pressure could be below the standard expected as well as not being powered to detect differences in these secondary outcomes. Even so, a review of this type, with pooled estimates from meta-analysis of more than 1000 participants in total, is able to detect small consistent differences. Many of the studies did provide information on how blood pressure was measured and some followed a published protocol so it is unlikely that blood pressure was poorly measured.

As many of the markers of CVD are related to weight it was difficult to isolate the contribution of the type of diet, in this case the GI, as separate from changes in weight. It cannot be ruled out that weight loss, at least in the short term, is explaining some of the beneficial effects of a low GI diet on blood pressure.

Within the trials there was some variation in the methods used to calculate GI and GL. Accordingly, the individual author definitions of high and low GI and GL have been adopted to compare studies, even when the apparent differences between trial arms appear to be quite small or not in accord with notions of what may be viewed as high or low. Unless tightly controlled in an experimental situation, in most cases high and low GI and GL diets differ in many ways other than the carbohydrate fraction, including dietary protein and fiber content, energy density and sensory quality. The review may have excluded informative studies shorter than 6 weeks in duration such as the Omnicarb trial(54), however there is no universally agreed upon length of follow up and the pragmatic length of 6 weeks was selected in advance for this study. In addition the review did not include children and adolescents and therefore the results from this review cannot be extrapolated to younger age groups.

Policy implications

Systematic reviews of the associations between fiber and blood pressure and lipids report similar or smaller effects on health than this review(55-57) and therefore it is possible that lower glycemic diets do offer a further beneficial effect over and above a high fiber and low fat diet by encompassing benefits from many components. However, it is not clear exactly which components of a low GI diet are responsible for the improvements in blood pressure. Indeed, there was no strong evidence of a dose response. Advising on a low GI diet to healthy individuals is more complex than describing a high fiber diet but lower glycemic diets are generally rich in high soluble fiber foods such as oats, beans, pulses, vegetables and whole fruits and low in sweetened drinks. High quality research in normal weight individuals is needed to enable the contribution of dietary manipulation to markers of CVD to be established, independent of weight changes before inclusion of a low GI diet in nutrition policy.

Conclusion

In relatively healthy individuals, lower glycemic diets are associated with significantly better profiles of blood pressure, although no clear dose response was apparent in these analyses. Furthermore, many of the trials included in the review aimed to reduce weight in participants making it difficult to isolate the impact of diet on blood pressure. The trials were also subject to considerable sources of bias, as is often the case in trials involving food-based interventions. Before lower glycemic diets are universally recommended by health professionals, high quality trials in healthy normal weight populations are needed to determine the effects of GI on blood pressure independent of weight change.

Acknowledgments

VJB was the project lead for the main systematic review concerning dietary carbohydrates and cardio-metabolic health and developed the research plan. All authors conducted the research as follows. VJB, DET, CLC searched databases, CPG helped develop search strategies, article screening was undertaken by VJB, DET, CLC and CELE and data extraction was carried out by VJB, DET, DCG, CLC and CELE. Quality of data extraction and checking was carried out by DET, CLC and CEW. Ms Camilla Nykjaer and Ms Charlotte Woodhead also contributed to data extraction and checking. Statistical analysis was undertaken by CELE and overseen by DCG. CELE wrote the first draft of the manuscript. All authors reviewed the manuscript and contributed to manuscript revisions and VJB had primary responsibility for final content.

The authors thank Charlotte Woodhead and Camilla Nykjaer for their contributions to data extraction and checking, James Thomas for his work developing the database into which all articles were extracted and Dr David Haughton for his advice on mechanisms of GI on blood pressure.

VJB, DET, CLC, CPG, CELE and DCG had no financial or personal relationships with the Department of Health for England during the project and no conflicts of interest to declare.

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Table 1: Trial characteristics for studies included in the meta-analysis on GI/GL and blood pressure

Authors, year, country and study name	Characteristics of participants (mean)	Intervention duration		Intervention description for each group	Actual diet characteristics, Macronutrient intake, energy intake and fiber	GI[1]/GL[2] value (scale) [3]	Group weight change	Weight change difference (positive = greater loss in low GI)
(Abete et al., 2008) (37) Spain	56% Male Age: 36 BMI: 32	8 weeks	Lower GI (n=32)	Energy restricted. Individually prescribed diet within a strict dietary frame-work repeated on a 3 day rotation basis. 84% of CHO provided by pasta and legumes.	%Energy[4]: C[5] 50, P[6] 18, F[7] 32 Fiber: 24.9g/d[8]	GI 40-45 (bread)	-7.5%	2.2%
			Higher GI (n=32)	Energy restricted. Individually prescribed diet within a strict dietary frame-work repeated on a 3 day rotation basis. 84% of CHO provided by rice and potatoes.	%Energy: C 48, P 20, F 33 Fiber: 18.5g/d	GI 60–65 (bread)	-5.3%	
(Bellisle et al., 2007) (31) France	0% Male Age range: 20 - 72 BMI range: 25 - 40	12 weeks	Lower GI (n=96)	Weight watchers program with a focus on low GI foods.	Not reported	Not reported (bread)	-1.5kg	-0.2kg
			Higher GI (n=65)	Weight watchers program.	Not reported	Not reported (bread)	-1.7kg	
(Buscemi et al., 2013)(38) Italy	48% Male Age: 50 BMI: 34	3 months	Lower GI (n=47)	Diet containing low GI foods such as pasta, wholegrain, yoghurt, legumes, peaches, apples, pears and oranges.	%Energy: C 55, P 20, F 25 Fiber: 32g/d	GI 44 GL 96 (n/a)	-8.3kg	1.2kg
			Higher GI (n=40)	Diet containing high GI foods such as rice, white bread, cornflakes, mashed potato, grapes and bananas.	%Energy: C 57, P 19, F 24 Fiber: 33g/d	GI 54 GL 124 (n/a)	-7.1kg	
(Ebbeling et al., 2005)(34) USA	12% Male Age: 28 BMI: overweight/	6 months intensive	Lower GI/GL (n=34)	Ad libitum low GI food.	%Energy: C 47, P 21, F 33 Energy 1391 kcal/d Fiber:20.7g/d	GI 46 GL 53 (g/1000kcal) (glucose)	-7.8kg	1.7kg

Authors, year, country and study name	Characteristics of participants (mean)	Intervention duration		Intervention description for each group	Actual diet characteristics, Macronutrient intake, energy intake and fiber	GI[1]/GL[2] value (scale) [3]	Group weight change	Weight change difference (positive = greater loss in low GI)
	obese		Higher GI/GL (n=24)	Lower fat diet. Meal plans based on an exchange system, energy deficit of 250-500kcal/d.	%Energy: C 59, P 19, F 23 Energy 1409 kcal/d Fiber:17.8g/d	GI: 53 GL: 77 (g/1000 kcal) (glucose)	-6.1kg	
(Ebbeling et al, 2007)(39) USA	21% Male Age: 28 BMI: >30	6 months	Lower GL (n=73)	Advice to consume low GL foods such as non-starchy vegetables, legumes and temperate fruits and to limit refined grains, starchy vegetables, fruit juices and sweets		GI: 45 GL: 30 (glucose)		0.5kg
			Higher GL (n=66)	Low fat diet. Advice to consume low-fat grains, vegetables, fruits and legumes and to limit added fats, high fat snacks and sweets.		GI: 55 GL: 70 (glucose)		
(Fava et al, 2013)(40) UK RISCK trial	49% Male Age: 54 BMI: 29	24 weeks	Lower GI/GL (n=88)	2. High monounsaturated low GI: Target as %E, F 38, SF 10, MF 20, PF 6, C 45, GI 53%	High MF low GI: Energy 2019kcal/d %Energy: C 46, P 17, F 35 Fiber: 20g/d	GI: 54 (bread)	0.2kg	
				4. High carbohydrate low GI: Target as %E, F 28, SF 10, MF 11, PF 6, C 55, GI 51%	High C low GI Energy: 1854kcal/d %Energy, C 55, P 18, F 23 Fiber: 22g/d	GI: 56 (bread)	-0.8kg	
			Higher GI/GL (n=77)	1.Higher monounsaturated high GI: Target as %E, F 38, SF 10, MF 20, PF 6, C 45, GI 64%	High MF high GI: Energy: 2056kcal;/d %Energy: C 43, P 16, F 38 Fiber: 19g/d	GI: 66 (bread)	0.4kg	

Authors, year, country and study name	Characteristics of participants (mean)	Intervention duration		Intervention description for each group	Actual diet characteristics, Macronutrient intake, energy intake and fiber	GI[1]/GL[2] value (scale) [3]	Group weight change	Weight change difference (positive = greater loss in low GI)
				3. High Carbohydrate high GI: Target as %E, F 28, SF 10, MF 11, PF 6, C 55, GI 64%	High C high GI Energy 1645kcal/d %Energy: C 51, P 20, F 27 Fiber: 17g/d	GI: 66 (bread)	-1.8kg	
(Gogebakan et al, 2011)(29) Germany DiOGenes study	36% Male Age: 41 BMI: 34	26 weeks	Lower GI (n=773)	Low protein, low GI: Target %Energy, F 23-28, C 57-62, P 10-15 High protein, low GI Target %Energy, F 23-28, C 45-50, P23-28	Not reported	Target GI 15% lower than high GI (glucose)	Low P, Low GI: 0.27kg High P, Low GI:-0.38kg	
			Higher GI (n=487)	Low protein, high GI: Target %Energy, F 23-28, C 57-62, P 10-15 High protein, high GI: Target %Energy, F 23-28, C 45-50, P 23-28,	Not reported	Target GI 15% higher than low GI (glucose)	Low P, High GI:1.45kg High P, High GI: 0.36kg	
(Jensen et al., 2008)(36) Denmark The Danish GI study	0% Male Age: 20 - 40 BMI: 28	10 weeks	Lower GI (n=55)	Received low GI test foods in place of their usual CHO rich foods.	%Energy: C 81, P 13, F 6 Energy: 4860kJ/d Fiber: 29g/d	GI: 72 (glucose)	-2kg	0.7kg
			Higher GI (n=44)	Received high GI test foods in place of their usual CHO rich foods.	%Energy: C 82, P 13, F 6 Energy: 4886kJ/d Fiber:32g/d	GI: 95 (glucose)	-1.3kg	
(Maki et al., 2007) (19) USA	33% Male Age: 50 BMI: 32	36 weeks	Lower GL (n=86)	Dietary advice ad libitum reduced-GL foods	g/d: C 69 P 97 F 80 Energy: 1365 kcal/d Fiber: 11g/d	GI: 48 GL: 8173 (bread)	-4.5kg	1.9kg

Authors, year, country and study name	Characteristics of participants (mean)	Intervention duration		Intervention description for each group	Actual diet characteristics, Macronutrient intake, energy intake and fiber	GI[1]/GL[2] value (scale) [3]	Group weight change	Weight change difference (positive = greater loss in low GI)
			Higher GL (n=84)	Higher GL, lower fat: Reduce fat intake, decrease portion sizes, target energy deficit 500-800 kcal/d	g/d: C 168, P 75, F 62 Energy: 1525 kcal/d Fiber: 12g/d	GI: 51 GL: 12118 (bread)	-2.6kg	
(Melanson et al, 2012)(32) USA	12% Male Age: 39 BMI: 31	12 weeks	Lower GI (n=157)	Wholegrain foods such as whole grain cereals, whole grain pasta, oatmeal, whole grain bread and refined grains used sparingly.	%Energy: C 49, P 23, F 30 Energy: 5878kJ/d Fiber: 14g/d	GI: 42 GL: 45 (bread)	-3.4kg	-0.3kg
			Higher GI (n=85)	Dietary advice to follow Weight Watchers diet based on points aiming to control portions rather than food types	%Energy: C 47, P 20, F 31 Energy: 5772kJ/d Fiber 13g/d	GI: 47 GL: 42 (bread)	-3.7kg	
(Pereira et al., 2004)(18) USA	23.7% Male Age: 31 BMI: overweight/ obese	Low GL: 65 days Low fat: 69days	Lower GI (n=46)	Energy restricted low glycemic load diet (60% of predicted requirements).	%Energy: C 43, P 27, F 30 Energy: 1500 kcal/d Fiber: 32g/d	GI: 50 GL: 82 (bread)	-1.1kg/wk	0.1kg
			Higher GI, lower fat (n=34)	Energy restricted low fat diet (60% of predicted requirements). NCEP Step 1 diet	%Energy: C 65, P 17, F 18 Energy: 1500 kcal/d Fiber: 20g/d	GI: 82 GL:205 (bread)	-1.0kg/wk	
(Philippou et al., 2009a)(35) UK	100% Male Age: 35 - 65 BMI: not reported	6 months	Lower GI (n=56)	Carbohydrate foods (e.g. seeded bread, wholemeal pita, muesli, porridge, sweet potatoes, pasta, noodles, basmati slow-cook rice, beans, lentils, apples, dried fruit, and nuts). Decreased Energy Intake.	g/d: C 224	GI: 51 GL: 114 (glucose)	-2.3kg	0.7kg

Authors, year, country and study name	Characteristics of participants (mean)	Intervention duration		Intervention description for each group	Actual diet characteristics, Macronutrient intake, energy intake and fiber	GI[1]/GL[2] value (scale) [3]	Group weight change	Weight change difference (positive = greater loss in low GI)
			Higher GI (n=31)	Carbohydrate foods (e.g. white/wholemeal bread, cornflakes, Weetabix, potatoes, couscous, risotto rice, melon, pineapple, rice cakes). Decreased Energy intake.	g/d: C 278	GI: 63 GL: 175 (glucose)	-3.0kg	
(Randolph et al, 2014)(41) USA	19% Male Age: 48 BMI: 30	12 weeks	Lower GI (n=90)	Advice on low GI foods, potatoes were provided on a weekly basis providing 5-7 portions per week. Target of GI=30	g/d: C 219, P 79, F 49 Fiber: 24g/d	GI: 52 GL: 106 (n/a)	-1.8kg	-1kg
			Higher GI (n=49)	Advice on high GI foods, potatoes were provided on a weekly basis providing 5-7 portions per week. Target of GI=80	g/d: C 197, P 73, F 53 Fiber: 23g/d	GI: 53 GL:103 (n/a)	-2.8kg	
(Venn et al, 2010)(30) New Zealand	14% Male Age: 42 BMI:35	6 months (intensive, 18 months overall)	Lower GI (n=113)	Instructed to eat 2 x 90g portions of pulses in place of 2 portions of bread or cereals and only wholegrain bread and cereals. Participants were supplied oats, wholemeal bread and pulses (canned).	%Energy: C 52, P 21, F 25 Energy: 5917kJ/d Fiber: 28g/d	GI: 47% GL: 92g (bread)	-7kg	0.2kg
			Higher GI (n=108)	Instructed to eat refined bread and cereals. Participants supplied with cornflakes, white bread and cans of tomatoes and corn.	%Energy: C 54, P 20, F 25 Energy: 6120kJ/d Fiber: 21g/d	GI: 51% GL: 108g (bread)	-6kg	

[1]GI=glycemic Index
[2]GL=glycemic load
[3]Scale for measuring GI (glucose or white bread)
[4]%E= percent energy
[5]C and CHO=carbohydrate

[6]P=protein
[7]F=fat
[8]g/d=grams per day

Table 2 RCT sources of bias for each study included in the meta-analysis

Authors	Allocation sequence generation	Allocation concealment	Participant blinding	Researcher Blinding	Incomplete outcome reporting	Selective outcome reporting	Any other bias
Abete et al 2008(37)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
Bellisle et al 2007 (31)	Unclear	Unclear	Bias	Bias	No Bias	No Bias	No Bias
Buscemi et al 2012(38)	No Bias	Unclear	Bias	No Bias	No Bias	No Bias	No Bias
Ebbeling et al 2007 (39)	No Bias	No Bias	Bias	No Bias	No Bias	No Bias	No Bias
Ebbeling et al 2005 (34)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
Fava et al 2013(40)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
Gogebakan et al 2011(29)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
Jensen et al 2008 (36)	No Bias	Unclear	No bias	No bias	No Bias	No Bias	No Bias
Maki et al 2007 (19)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
Melanson et al 2012(32)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
Pereira et al 2004 (18)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
Philippou et al 2009a (35)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
Randolph et al 2014(41)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
Venn et al 2010(30)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias

Table 3: Meta-regression and sub-group analyses using random effects models indicating the coefficient for change in blood pressure (pooled estimate for sub-group analysis) in mmHg together with 95% confidence intervals, p values and residual I^2 for each higher unit of variable including GI units, age, BMI, energy and macronutrients. Results for differences in energy intake (EI) are per 100kcal. Results for comparison between high and low differences in GI are the differences in BP between 9 studies in the higher difference category and 6 studies in the lower difference in GI category (a positive BP coefficient indicates that BP is higher with a larger difference in GI between the low and high GI diets) .

Variable	Outcome	No. studies	BP estimate (mmHg/unit)	95% CI (mmHg/unit)	P value	(Residual) I^2 (%)
Difference in GI units between arms (results using original scale reported)	SBP	15	0.06	-0.10 to 0.22	0.42	2.9
	DBP	15	0.07	-0.06 to 0.20	0.29	13.9
Difference in GI units between arms (results with bread scale converted to glucose scale)	SBP	15	0.01	-0.18 to 0.20	0.89	1.6
	DBP	15	0.05	-0.11 to 0.21	0.50	10.8
Difference between high (>10 units) and low (0-10 units) arms	SBP	15	-0.19	-3.12 to 2.75	0.89	1.6
	DBP	15	0.60	-1.78 to 2.99	0.59	13.0
Subgroup analysis: trials with differences of 1 to 10 units of GI (converted to glucose scale)	SBP	9	1.52	-0.42 to 3.47	0.13	0
	DBP	9	1.03	-0.38 to 2.43	0.15	0
Subgroup analysis: trials with differences of 12-23 units of GI (converted to glucose scale)	SBP	6	1.69	-0.92 to 4.30	0.20	47.8
	DBP	6	1.84	0.27 to 3.40	0.02	40
Difference in mean age at baseline (years)	SBP	14	0.03	-0.18 to 0.24	0.75	14.0
	DBP	14	0.03	-0.13 to 0.19	0.69	24.8
Difference in BMI at baseline (kg/m^2)	SBP	11	-0.13	-0.83 to 0.57	0.69	0
	DBP	11	-0.46	-1.02 to 0.11	0.10	8.4
Difference in weight change between groups (kg) (a positive value indicates more weight loss in low GI arm)	SBP	14	-0.21	-2.05 to 1.63	0.81	14.2
	DBP	14	0.09	-1.39 to 1.58	0.90	24.8
Difference in adherence monitoring reported (not reported is reference category)	SBP	16	-1.36	-4.62 to 1.90	0.39	10.7
	DBP	16	-1.54	-4.00 to 0.92	0.20	14.9
Difference in Energy intake reported between groups (per 100Kcal)	SBP	8	-2.11	-5.57 to 1.36	0.19	0
	DBP	8	-0.87	-3.39 to 1.65	0.43	0
Difference in protein intake reported between groups (% EI)	SBP	10	-0.05	-0.52 to 0.43	0.83	0
	DBP	10	-0.11	-0.48 to 0.26	0.51	0
Difference in fat intake reported between groups (% EI)	SBP	10	0.02	-0.29 to 0.32	0.90	0
	DBP	10	-0.05	-0.29 to 0.18	0.62	0
Difference in fiber intake reported between groups (g)	SBP	10	-0.20	-0.58 to 0.18	0.26	0
	DBP	10	0.02	-0.29 to 0.34	0.87	0

Figure Legends

Figure 1: Flowchart to indicate number of studies included at each stage of the review

Figure 2: Difference in SBP (mmHg) between low GI diet and high GI diet. The forest plot displays the weighted difference in means, 95% CI for difference in means and unit difference in GI index between groups for each study.

Figure 3: Difference in DBP (mmHg) between low GI diet and high GI diet. The forest plot displays the weighted difference in means, 95% CI for difference in means and unit difference in GI index between groups for each study.

Figure 4: Funnel plot for SBP and studies reporting difference in GI or GL between groups

Figure 5: Funnel plot for DBP and studies reporting difference in GI between groups

Figure 6: Difference in SBP (mmHg) between low GL diet and high GL diet. The forest plot displays the weighted difference in means, 95% CI for difference in means and grams difference in GL index between groups for each study

Figure 7: Difference in DBP (mmHg) between low GL diet and high GL diet. The forest plot displays the weighted difference in means, 95% CI for difference in means and grams difference in GL index between groups for each study