THE CARB-APPROPRIATE REVIEW

A MONTHLY RESEARCH REVIEW BY

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ABOUT CLIFF

Cliff Harvey PhD is an author, clinician, and researcher. He was one of the first clinical nutritionists to begin working with ketogenic and low-carb diets, way back in the 1990s and is also considered a pioneer in the area of mind-body integrative healthcare.

Cliff's early post-graduate work was in mind-body healthcare, while his master's research focussed on the use of medium-chain triglycerides to mitigate 'keto-flu' and encourage faster induction of nutritional ketosis.

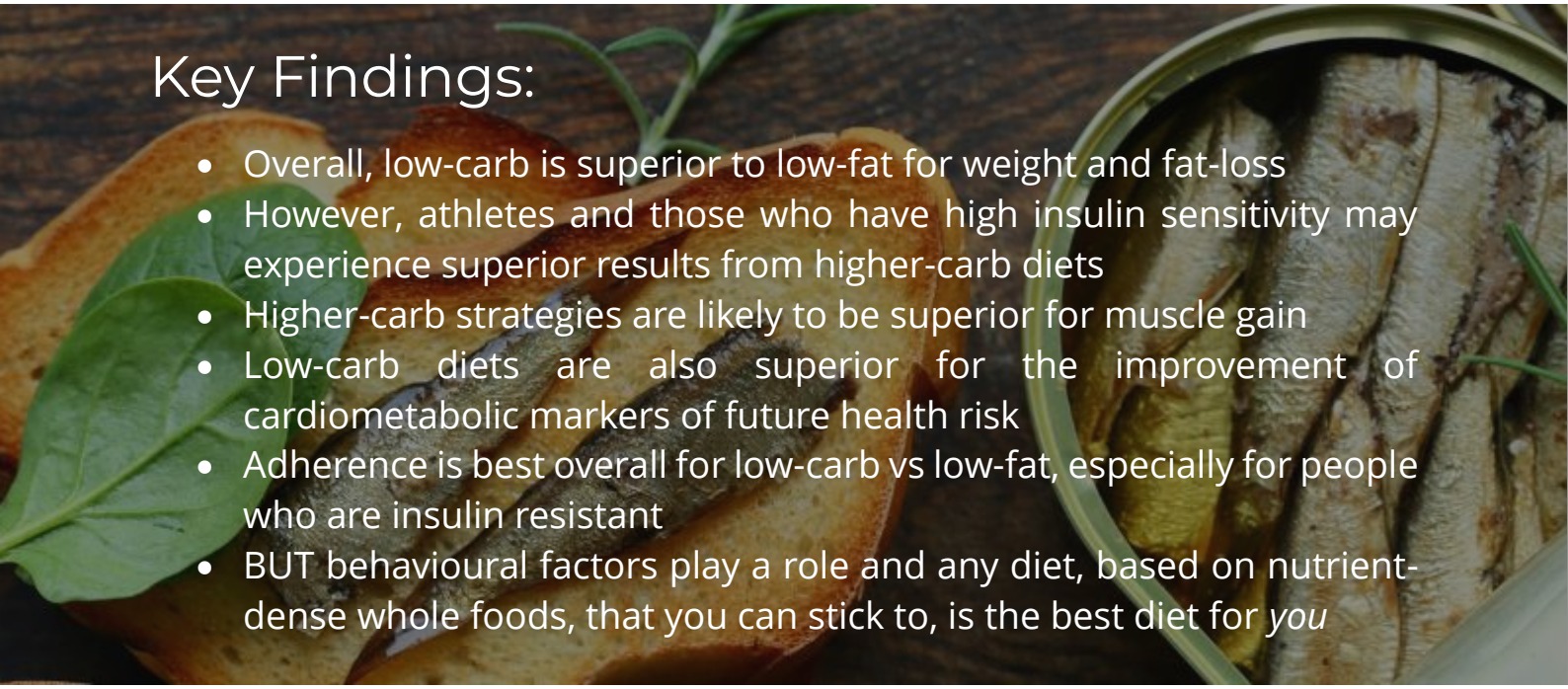
His doctoral thesis continued to investigate keto-flu and ketogenesis, and the effects of different types of low-carbohydrate diets along with the individualisation of dietary prescription and how 'carbohydrate tolerance' varies from person-to-person.

He is a former world champion strength athlete, submission grappler, and author of several best-selling books.

THIS MONTH

HIGH CARB OR LOW CARB?

Which should *you* choose for health?



Key Findings:

- Overall, low-carb is superior to low-fat for weight and fat-loss
- However, athletes and those who have high insulin sensitivity may experience superior results from higher-carb diets
- Higher-carb strategies are likely to be superior for muscle gain
- Low-carb diets are also superior for the improvement of cardiometabolic markers of future health risk
- Adherence is best overall for low-carb vs low-fat, especially for people who are insulin resistant
- BUT behavioural factors play a role and any diet, based on nutrient-dense whole foods, that you can stick to, is the best diet for *you*

There is a growing awareness, and rising use of low-carbohydrate diets for health conditions, most especially metabolic syndrome and related disorders, and increasing interest in their use for cancer treatment (covered in a previous issue of CARR). They are also becoming extremely popular in the mainstream. For example, in the first ¼ of 2019, four of five *Amazon* best-sellers in the 'Diet and Weight-loss' category were based on low-carbohydrate diet principles and a google search for "Low-Carbohydrate Diet" returned over 44,000,000 results. Despite this mainstream popularity, many important areas within this area suffer from a lack of relevant research and there are many misconceptions about the relative merits of low-carb vs high-carb diets.

There is also very conflicting advice as to who should (or should not) use either a lower- or higher-carb diet and who will benefit most from either approach. There has been limited research looking into the 'appropriateness' of diets more or less carb-restricted for individuals.

In this article, I summarise the available research to try to get to the bottom of who should use a low-carb diet...and who should stick to a moderate or even higher-carb one?

The relative effectiveness of low-carb vs high-carb

An idea commonly promoted is that over the long-term either low-carb or high-carb diets result in similar results for both weight and fat-loss. This is most likely true (again, based on the evidence available) but, on balance, low-carb might still provide greater benefits for certain outcomes and for many people when compared to high-carb, low-fat nutrition regimens.

> In studies up to 12 months, low-carb diets result in greater weight loss than low-fat diets

In studies up to 12 months, low-carb diets result in greater weight loss than low-fat. They also improve the key markers of future health risk; blood pressure, HDL cholesterol, and most importantly triglycerides ('fats' in the blood—probably the strongest indicator of future health risk of any common blood measure.) On the other hand, low-fat interventions result in improved LDL and total cholesterol,[1] which are indicators of future health risk, although in comparison to triglycerides, HDL, and other measures like blood glucose and insulin, are relatively weak. Low-carb diets also result in significant improvements in glycated haemoglobin and fasting glucose, insulin, and c-reactive protein (a key measure of systemic inflammation).[2]

However, after 12 months, the effect between higher- or lower-carb diets typically narrows, particularly for weight- and fat-loss, but there might be persistent benefits to cardiometabolic health (especially for improvements in triglycerides and HDL) from low-carb diets over these longer timeframes.[3-5]

Bueno and colleagues in their systematic review of 13 randomised controlled trials with greater than 12 months follow-ups, did, however, note greater overall weight loss from low-carb vs low-fat diets, along with improvements in cardiometabolic markers of health.[6] Similarly, Sackner-Bernstein et al., note *[low-carb diets are] associated with modest but significantly greater improvements in weight loss and predicted cardiovascular disease risk in studies from 8 weeks to 24 months in duration*.[7] In a review of 14 body composition change trials up to 2014, Hashimoto et al found that low-carb diets were associated with a significant

reduction in body fat but sub-group analysis suggested that the results were limited to *very* low-carb diets.[8]

On balance, the evidence from these reviews suggest that low-carb diets are likely to be more effective for weight and fat-loss than low-fat interventions in the short-term but over the longer term, the effect between different diets narrows. This further suggests that over the long term the diet that you can stick to is likely to be the best option! BUT if you can stick to a lower-carb (vs higher carb diet) over the long term that there could be slightly greater benefits for future health risk and if you follow a very-low-carb plan, there could be a greater effect on weight and fat-loss.

On balance, low-carb is better for fat loss and weight loss, especially over the short to medium term. It may not be superior to weight loss for insulin sensitive people and athletes though...

Who benefits most from higher-carb and lower-carb?

While reviews of the scientific evidence show that when calories are restricted equally, there is little difference in outcomes (including weight, total or LDL cholesterol, and diastolic blood pressure) for those with Type 2 diabetes over the long-term,[9-13] it is also well demonstrated that the greater the carbohydrate restriction, the greater the glucose-lowering effect,[12] and low-carb diets result in significantly greater improvements in HbA1c (a proxy measure of average blood glucose levels), and cardiovascular disease markers and risk indicators, specifically; HDL, and systolic blood pressure.[13]

In preliminary randomised controlled trials that had been performed, people with *relative* insulin resistance (IR) respond more favourably to a low-carbohydrate diet, while those people more insulin sensitive (IS) get better results from a higher carbohydrate diet.

> people with *relative* insulin resistance (IR) respond more favourably to a low-carb diet, while those people more insulin sensitive get better results from higher carbs

Four randomised controlled studies have looked specifically at this topic with several others offering tangential evidence. It is worth noting that these studies looked at *relative insulin resistance,* in other words, comparing those participants who were most insulin sensitive vs those least, not those

diagnosed as insulin resistant (who are most likely to have the greatest benefits from a low-carb diet).

Pittas and colleagues demonstrated that those with above-median insulin response (i.e. were more insulin resistant) lost more weight when consuming a low-carb diet compared with a high-carb one ($p < 0.05$).[14] The reverse was observed in the more insulin sensitive group, who lost more weight following a high carb diet (but this difference was not statistically significant ($p = 0.25$)).

Similar results were demonstrated in a study comparing obese, nondiabetic insulin-sensitive women to obese, nondiabetic insulin-resistant who were randomised to receive either a high-carb, low-fat diet (60% carbs, 20% fat) or lower-carb, higher-fat (40% CHO, 40% fat). Insulin-sensitive women lost twice as much weight on a high-carb diet compared to low-carb ($p < 0.002$ between the groups). In contrast, insulin-resistant women lost approximately 50% more weight on the low-carb diet compared to the higher-carb ($p < 0.04$ between two groups).[15] Likewise, in a 6-month, randomised controlled trial of 73 obese young-adults, a lower-carb diet (40% carbohydrate and 35% fat) was compared to a low-fat (55% carbohydrate and 20% fat) diet. While there was little difference between the two groups overall, those in the low-carb group that displayed higher than average insulin responses to a glucose challenge (i.e. the 'more' insulin-resistant participants) had a greater reduction in weight and body fat than those in the low-fat group at 18 months.[16] Similarly, in another study (of 245 overweight and obese women), while there was no significant difference in weight loss between lower and higher carbohydrate diet groups overall, insulin-sensitive participants achieved greater weight loss on a higher carbohydrate diet.[17] A pilot trial to investigate these effects in an *ad libitum* (eat as much as desired) diet over six-months found increased weight loss resulting from low-carbohydrate diets in insulin-resistant participants and improved weight loss resulting from low-fat diets for insulin-sensitive participants, with these results failing to reach significance. Also noted were (non-significant) improvements in HDL, triglycerides, fasting glucose and insulin, and blood pressure for low-carb diets versus high-carb in those more insulin resistant. In those more insulin sensitive, the low carbohydrate diet improved HDL and triglycerides more than that of the low-fat diet, whereas the low-fat diet resulted in improved fasted insulin and glucose.[18]

While not specifically addressing insulin resistance vs sensitivity, an RCT conducted by Tay and colleagues suggested improved outcomes for triglycerides and HDL, from a very low carb diet vs high carb diet, with no change in LDL cholesterol and no

difference in weight loss, in a cohort of abdominally obese participants (who are also likely to be insulin resistant).[19] While, a recent study on increased energy expenditure related to baseline insulin homeostasis by Ebbeling et al., [20] suggest that the carbohydrate-insulin interaction is a modifier of dietary outcomes and that lower-carb diets might result in increased 'burn' of energy (thereby contributing another element to the fat-loss picture).

Taken on balance, these results suggest that those who are more insulin resistant and those with metabolic syndrome (pre-diabetes) will achieve better results from low-carb diets and conversely, those who are insulin sensitive might actually achieve *better* results for weight- and fat-loss and for improvement of cardiometabolic risk-markers from higher-carb and lower-fat diets. It is important to note that these studies typically compared only moderate reductions in carbohydrate (with 'low-carb' being ~40% of calories from carbohydrate) which most of us would not consider to be 'functionally' low-carb and yet even these moderate restrictions resulted in significant improvements for those people who are more insulin sensitive. Because other research (and now our research out of AUT University) has suggested that greater improvements are likely to result from the greater restriction of carbs for these people, more research needs to address this.

What about the DIETFITS study? Didn't that put the 'nail in the low-carb coffin'?

While the previous research suggested that people who are more insulin sensitive benefit more from higher-carb diets and those who are more insulin resistant benefit more from lower-carb, the recent DIETFITS study by Gardner et al., cast some doubt on this and was widely reported in the media as the 'nail in the low-carb coffin'. In fact, the study concluded that *there was no significant difference in weight change between a healthy low-fat diet vs a healthy low-carbohydrate diet, and neither genotype pattern nor baseline insulin secretion was associated with the dietary effects on weight loss.* [21]

But does this tell the whole story?...

The DIETFITS study IS a great addition to the body of evidence. It was a large intervention study with over 600 participants. It was well-funded, a randomised controlled trial, and it compared two healthy diets (many studies compare standard poor diets to intervention diets) over a relatively long timeframe (12 months). However, it also used an interesting methodology; beginning with a baseline diet containing either 20 g of fat per day in the low-fat and 20 g of carbohydrate per day in the low-carb group. Participants were then instructed to gradually increase their daily intake of either fat or carbohydrate by 5 g (fat) or 15 g (carbs) per week until

they found the *lowest level of intake they believed could be maintained.* This led to a relatively modest carbohydrate restriction overall in the low-carbohydrate group; consuming 26.5% calories from carbs compared to the low-fat diet group which consumed 50.6%. It should also be considered that the protein intake was modest at less than 1 g protein per kg of body weight per day. So, perhaps it's fairer to say that DIETFITS compared a healthy lower-fat diet to a healthy moderately carbohydrate-restricted diet and both diets were fairly low in protein. It was also a study in relatively healthy overweight volunteers, and so, the people who were excluded were exactly those who would be likely to benefit most from lower-carb i.e. those with *"hypertension or metabolic disease; diabetes; cancer; heart, renal, or liver disease"*

The low-fat group lost 5.3 kg (95% CI, -5.9 to -4.7), while the low-carb group lost -6.0 kg (95% CI, -6.6 to -5.4). This is a small difference and while it did not meet the threshold for significance (p = 0.13) the mean weight-loss in the lower-carbohydrate group was greater than the 95% CI threshold of the lower-fat group. This does suggest that the odds against chance are that there will be greater weight and fat-loss on a lower-carbohydrate diet and particularly so given the relatively modest difference in carbs between the groups. This trend towards greater fat- and weight-loss has been demonstrated in the majority of studies summarised in systematic reviews and meta-analyses, suggesting that there is a greater chance of improved fat-loss overall from carbohydrate-restricted diets. This implication is further strengthened by significantly greater improvements in BMI (0.33, 95% CI 0.01 to 0.64, p = 0.04), along with a greater reduction in waist circumference (0.67 95% CI −0.60 to 1.94), body fat % (0.18 95% CI −0.40 to 0.75), and blood pressure (0.54, 95% CI −1.07 to 2.16), and improved respiratory quotient (0.020, 95% CI 0.006 to 0.033) resulting from the lower-carb diet compared to the higher-. While these results are, on the whole somewhat equivocal, it is interesting to note that 9 of 13 reported variables were improved more by low carb than low-fat.

Consistent with the existing research, there were significant between-group differences for LDL cholesterol favouring the low-fat group (-2.12, 95% CI -4.70 to 0.47); (low carb: 3.62, 95% CI 1.04 to 6.19). However, both triglycerides and HDL cholesterol were improved significantly more by the lower-carb diet.

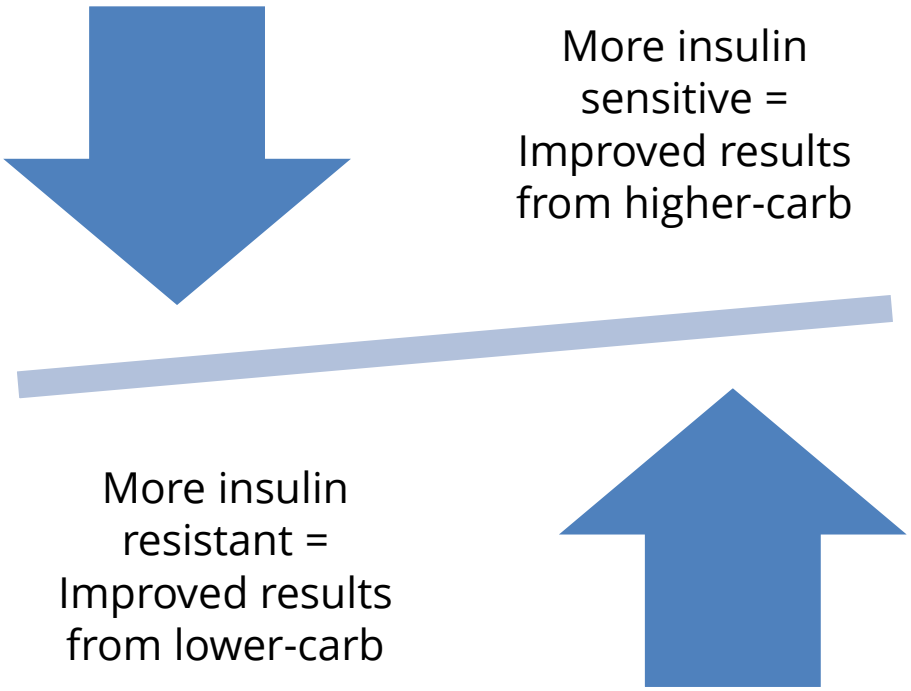
There was a nearly 3-fold greater improvement in triglycerides in lower-carb vs low-fat and a 7-fold improvement in HDL for the lower-carb group!

As I have previously mentioned, significant improvements in HDL cholesterol and triglycerides are clinically more meaningful than relatively minor changes in total or LDL cholesterol.

Dietary interventions that reduce serum cholesterol levels do not result in significant differences in either cardiovascular disease mortality or all-cause mortality.[22] Conversely, increased triglyceride levels show a linear association with a higher risk of cardiovascular disease and all-cause mortality.[23]

Overall, the multiplicity of benefits resulting from the lower-carb diet in DIETFITS shows a strong trend towards it being *possibly* more effective overall for both weight and fat-loss, and more effective for the improvement of the most important predictors of cardiovascular and all-cause mortality.

Optimal carb intake is likely to be affected by how insulin sensitive vs resistant you are. More insulin-resistant = lower-carb, more insulin sensitive = higher-carb



Can baseline blood measures predict the diet you should follow?

In an upcoming publication, we will present data from a pilot study which suggests a hypothesis that a combination of baseline cardiometabolic indicators, especially triglycerides and HDL cholesterol, have predictive value for which type of diet someone should be on. In essence, the 'worse' your baseline lipid profile (i.e. someone in poorer metabolic health), the more likely you are to benefit from a very low-carbohydrate diet, conversely, the 'better' your baseline cardiometabolic profile, the more likely you might benefit from a higher-carbohydrate approach. For example, we saw a trend towards greater associations between baseline TG-HDL ratio and improvements in TG-HDL concomitant to the magnitude of carbohydrate restriction; β -0.24, -0.9, and -0.95 for diets containing 25%, 15% and 5% TE from CHO respectively over a 12-week period. This also suggests that as one's health improves; they will become more tolerant of (and even benefit from) increased levels of carbohydrate in the diet.

It's likely that the 'worse' your baseline triglyceride levels, the more you should restrict carbs.

Could a 'Carb-Tolerance Questionnaire' predict whether you should follow a higher or lower-carb diet?

Clinicians often utilise a variety of questions, based on commonly reported effects of poorer 'carb-tolerance' like dips in energy after eating a high-carb meal, excessive cravings or desire for sugar and high-carb foods, mood or mental disturbance from higher-carb foods, and self-reported weight gain (especially middle weight gain) as a result of eating higher-carb foods. But, at this time, there is little research available to support the use of questionnaires to indicate whether a lower- or higher-carbohydrate diet is a 'best-fit' for an individual. For example, 'metabolic type' has been suggested in books and articles as a predictor of which type of diet someone should follow,[24] but a pilot trial of rugby players in New Zealand found that the metabolic type questionnaire results did not match up with laboratory analysis of fat and carbohydrate oxidation rates.[25]

We recently published the results of a pilot study on a proposed 'Carbohydrate Tolerance Questionnaire'.[26] This questionnaire used the following questions:

- *When I gain weight, I tend to put it on my tummy / around my middle*
- *If I don't eat regularly / every few hours I suffer energy 'crashes', or mood / mental disturbance [i.e. 'hangry'],*
- *I crave sweet and/or starchy foods often*
- *I snack on sugary or starchy food to relieve headaches/irritability/ craving/excessive hunger*

Answers were ranked on a 5-point scale of: Not at all, Seldom, Occasionally, Often, Almost always.

Overall, we demonstrated that people with higher baseline 'Carb Intolerance Scores' (who we suspected would do 'worse' on a higher carb diet) had the best results for improvements in key measures like triglycerides and HDL cholesterol from a low-carb diet intervention. However, results between different low-carb diets (ranging between 25% calories from carbs, down to 5% calories from carbs) didn't differ significantly. So, although those with worse self-reported responses to carbs tended to do better on a low-carb diet intervention, we can't be sure at this time whether they benefit most from a greater restriction of carbs, or whether perhaps they simply benefited most from following a good diet because they were most sensitive to higher intakes of ultra-refined and processed foods and/or were more metabolically challenged. In a retrospective analysis, I also found that there was no meaningful or significant association between baseline, self-reported 'carb-intolerance' and any body, or blood measurement.

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Questionnaires to predict macro allocation require further research.

How does adherence affect which diet you should follow?

It is a common narrative in the mainstream AND scientific media that low-carbohydrate diets are difficult to stick to. However, this is actually not matched by the evidence.

A systematic review of long-term (6-36 month) low-carbohydrate diets vs low-fat, calorie-restricted diet interventions showed an overall attrition rate of 36%, with a higher rate of attrition in low-fat, high-carbohydrate interventions (Figure 1.)[3] In these studies, 11 of 13 compared *ad libitum* lower-carbohydrate (and higher-protein) diets to calorie-restricted higher-carbohydrate diets. The higher

adherence rates to low-carb were not likely to be due to simply eating more, as the data favoured improved weight and fat-loss results in the low-carb diets, and improved results for HDL, triglycerides, and blood pressure. Because the participants 'ate as much as they desired' and yet achieved better results for fat-loss, this supports the hypothesis that lower-carb, with higher-protein, provides an 'auto-regulation' effect that helps people to eat to comfort levels and yet not overeat.

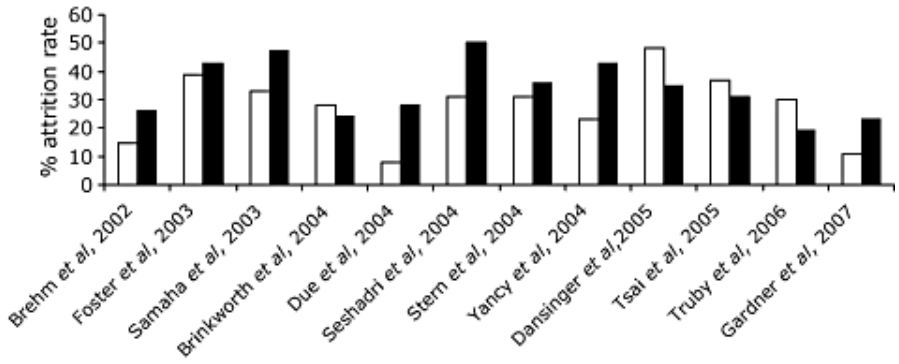

Figure 1. The percentage attrition rate in low-carbohydrate (white) and low-fat (black) diets reported in the literature. A systematic review of randomized controlled trials of low carbohydrate vs. low-fat/low-calorie diets in the management of obesity

It has also been demonstrated that insulin-resistant people are less likely to adhere and therefore to lose weight on a low-fat diet, compared to insulin-sensitive people. However, adherence and weight-loss were similar between both insulin resistant and sensitive participants allocated to a low-carb diet.[27] So, while low-carb is equally well adhered to, low-fat is more difficult to adhere to for those at increased risk of future cardio-metabolic events. Many of the (especially earlier) studies included in reviews and meta-analyses compare calorie-restricted high carbohydrate diets to ad libitum lower carbohydrate diets (such as those by Brehm et al.,[28] Ebbeling et al.,[29] and others).

insulin-resistant people are less likely to adhere and therefore to lose weight on a low-fat diet

People tend to adhere to low-carb diets better than low-fat, especially if insulin resistant.

Behavioural types and adherence

In a qualitative study arising from a ketogenic diet, controlled trial,[30] my colleagues and I reported a finding of very different behavioural patterns which we characterised as 'abstainers vs moderators'.

Some participants, while having enjoyed the study and the diet, sought advice for how they could moderate the diet post-intervention to make it more flexible, others were happy to continue with a strict compendium of foods (low-carbohydrate) that allowed relative freedom of choice within the compendium, as they felt that if they resumed eating carbohydrate foods, they would not be able to moderate. This could help to explain, conceptually and behaviourally, why different people respond better or worse to moderated diet plans vs inclusion/exclusion strategies.

Behavioural preferences (i.e. 'abstainers' or 'moderators') affect adherence.

Do activity and sport affect the type of diet I should be eating?

There is a finite amount of carbohydrate able to be stored in the body as glycogen. So, it has commonly been assumed that athletes should eat a high-carbohydrate diet to provide optimal stores of fuel for activity, especially intense 'glycolytic' (carb-burning) exercise.

Louise Burke, a renowned nutrition leader, famously called the 'nail in the coffin' for low-carb and performance several years ago and recently walked that back in response to growing anecdotal and clinical evidence that at least some athletes benefit from low-carbohydrate diets and that newer modifications to these diets might be appropriate for performance.[31]

Overall, the evidence shows little if any detriment to strength and power athletes from lower-carb regimens,[32] while studies have noted no-change or slight decrements in performance in endurance athletes over relatively short time-frames (i.e. circa 10-12 weeks), but with improvements in wellbeing, inflammation, and body-composition.[33] Stephen Phinney and others have suggested that given time for adaptation, optimised sodium and potassium provision and sufficient fat intake to provide for energy-sufficiency, there should be unimpaired endurance performance even if in ketosis resulting from a very-low-carb approach.[34, 35]

Are glycogen levels depleted in low-carbohydrate diets?

Reductions in glycogen have been noted in short-term studies on low-carb and keto diets,[36] but more recently in a long-term (20 month) study comparing a high carb (~60% calories from carbs) vs low-carb (~10% calories from carbs) diet in ultra-endurance athletes fat oxidation was higher overall and persisted at higher intensities of exercise [(figure X)] AND most importantly there were no appreciable differences in either resting muscle glycogen or the level of depletion after 180 min of running (− 64% from pre-exercise) and 120 min of recovery (− 36% from pre-exercise). The authors

concluded, *"Compared to highly trained ultra-endurance athletes consuming a high-carbohydrate diet, long-term keto-adaptation results in extraordinarily high rates of fat oxidation, whereas muscle glycogen utilization and repletion patterns during and after a 3-hour run are similar."*[37]

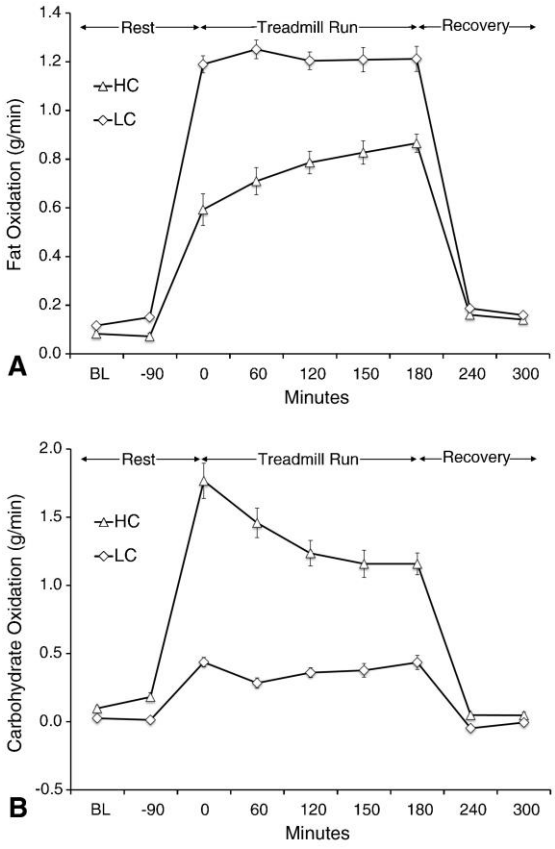

Figure 2. Increased fat vs carbohydrate oxidation in fat-adapted endurance athletes

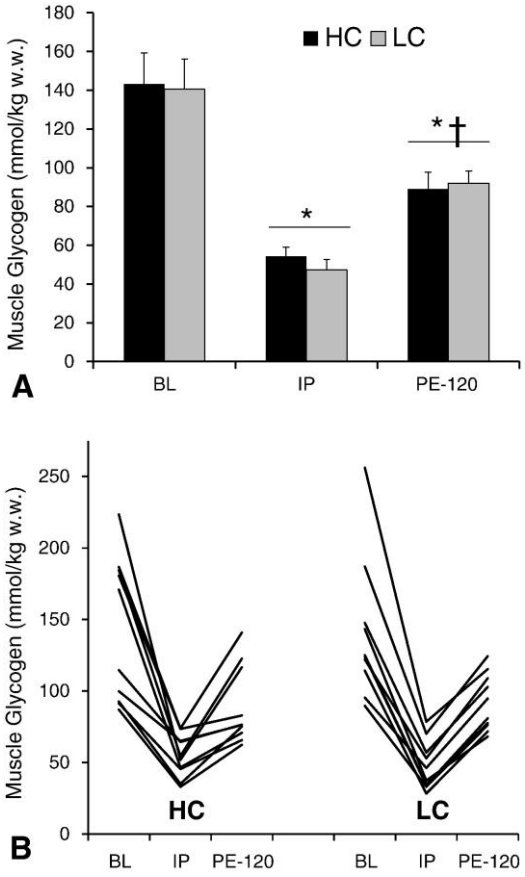

Figure 3. No difference in muscle glycogen between low-carb, high-fat and low-fat, high-carb athletes

Metabolic efficiency

Metabolic efficiency refers to the ability to use different fuels to maximise the ability of the body to efficiently perform during activities of differing intensities. Low-carb diets even without supplementation of either carbohydrate or ketones might be appropriate for recreational athletes or those involved in low-volume sports or training. For elite athletes, especially endurance athletes, periodised training with low carbohydrate diets, combined with carbohydrate and/or ketone supplementation is likely to be most appropriate.[38] The effect of a ketogenic diet in athletes is equivocal and

performance benefits vary substantially.[39]

Low-carb diets can result in equal glycogen storage HOWEVER all athletes, whether high or low-carb can deplete glycogen stores and high volumes of activity benefit from the addition of additional fuel overall, and additional carbohydrate (i.e. during and after long exercise bouts) to fuel benefit exercise.

Summary and conclusions

The evidence considered 'as a whole' shows that low-carb is likely to be superior for fat loss over low-fat diets. However, this may not apply to those who are very insulin sensitive and to athletes who are likely to be both insulin-sensitive and very active. On the other hand, muscle gain and retention benefit from the addition of carbohydrate to the diet.

Low-carb diets are also likely to be superior for the improvement of markers of future health risk, especially for those who are insulin resistant and who have 'worse' measures at baseline (such as poor glucose control or poor blood lipid readings).

Adherence might be better for low-carb over low-fat and this is especially true for those who are insulin resistant. Behavioural and psychosocial factors are also likely to play a key role in being able to comply with any diet too.

On balance, the best diet for *YOU* is still one that is calorie and protein sufficient, nutrient-dense, and *that YOU can stick to over the long term.* Over time, any differences between otherwise healthy diets are small and the biggest variations in results people derive from diet have a greater tie to behaviours, mindset, and the psychology of eating.

It's important to recognise that there is far more than just physical measures of outcomes too. How you *feel* on a particular diet and how it works within your psychosocial environment are also critically important. To paraphrase words from my friend and colleague, Professor Grant Schofield; "At the end of the day, the most important thing for most people is how they *feel*". How someone feels is not only important for their sense of wellness, satisfaction, health, and happiness in the moment, but will also likely affect adherence to a diet that will help them reduce their risk of future ill-health, and thus, has important implications for societal health. That's why differing diets have such avid devotees, because they have found something (for better, or for worse) that works for them, and for them, the n = 1 is all that matters!

IN THE LITERATURE

What is 'benevolent pseudo-diabetes'?

The mystery of the ketogenic diet: benevolent pseudo-diabetes

Mikhail Blagosklonny

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https://doi.org/10.1080/15384101.2019.1644765

Abstract

Designed a century ago to treat epilepsy, the ketogenic diet (KD) is also effective against obesity and diabetes. Paradoxically, some studies in rodents have found that the KD seemingly causes diabetes, contradicting solid clinical data in humans. This paradox can be resolved by applying the concept of starvation pseudo-diabetes, which was discovered in starved animals almost two centuries ago and has also been observed in some rapamycin-treated rodents. Intriguingly, use of the KD and rapamycin is indicated for a similar spectrum of diseases, including Alzheimer's disease and cancer. Even more intriguingly, benevolent (starvation) pseudo-diabetes may counteract type 2 diabetes or its complications.[40]

Comment

In this fascinating paper, Mikhail Blagosklonny discusses the conflict between the overwhelmingly positive effects seen from low-carbohydrate and ketogenic diets in metabolic syndrome and diabetes and the apparent *causing of metabolic syndrome* by these diets in some animal studies.

The suggestion has also been made repeatedly in the media that insulin resistance is caused by ketogenic diets (mainly demonstrated in animal studies) and this can be demonstrated in oral glucose challenge tests after a ketogenic diet in both animal and human subjects.

In the paper above, Blagoskonny discusses 'starvation diabetes', a condition observed in rabbits and dogs. This is observed to occur because with long-term starvation, despite ketones being produced, it is still desirable for the body to preserve glucose for use by the neurons of the brain and central nervous system and so, along with low insulin levels, insulin resistance goes up and this reduces the ability of tissue throughout the body to take up glucose, leaving it available for use by the brain. In other words, when there is both low overall fuel availability and low carbohydrate availability, the body will reduce the ability of tissue throughout the body to take up glucose, so as to preserve it for use by the brain and nervous system.

> when there is low fuel and carbohydrate availability, the body will reduce the ability of tissue throughout the body to take up glucose, to preserve it for use by the brain and nervous system

This 'starvation diabetes' can also be elicited by very low carbohydrate ketogenic diets, especially if also calorie restricted.

When starvation diabetes-like effects are observed as a result of a nutrient-replete ketogenic diet, it has been called 'benevolent pseudo-diabetes' and is actually believed to be protective against the typically observed negative effects of diabetes like neuropathy and retinopathy (amongst others) and is also quickly reversed upon resumption of eating a normal diet that is higher in carbohydrate content. Thus, this type of insulin resistance is an adaptation that helps, rather than hinders, and is quite different to the long-term insulin resistance caused by a diet rich in sugar and carbohydrate from ultra-refined foods and other negative lifestyle factors.

The take-home messages from this paper, matched to my clinical observations are several.

1. Humans and rodents are quite different. The conclusions from rodent studies on keto and low carb provide for hypotheses that should be investigated in humans. They should never be applied to humans independently as rodents basically suck at ketosis compared to humans!
2. Transient insulin resistance as shown by an oral glucose tolerance challenge after being on a keto-diet doesn't actually indicate insulin resistance present with metabolic syndrome, pre-diabetes and diabetes.
3. Benevolent pseudodiabetes provides benefits to animals and is likely to do the same for humans when in a calorie and carbohydrate-restricted state.

Another nail in the coffin for the saturated fat—heart disease hypothesis?

Dietary total fat, fatty acids intake, and risk of cardiovascular disease: a dose-response meta-analysis of cohort studies

Yongjian Zhu, Yacong Bo & Yanhua Liu

Lipids in Health and Disease | Volume 18, Article number: 91 (2019)

https://lipidworld.biomedcentral.com/articles/10.1186/s12944-019-1035-2?fbclid=IwAR0mFp2qUNCQjpDCtw8EgfllUTRv5vs1kfuCuUbmzJOqtVYf4-W20OYHVoA

Abstract

Background

Several epidemiological studies have investigated the association between dietary fat intake and cardiovascular disease. However, dietary recommendations based on systematic review and meta-analysis might be more credible.

Methods and results

Pubmed, Embase and Cochrane Library were searched up to July 1st, 2018 for cohort studies reporting associations of dietary fat intake and risk of CVDs. By comparing the highest vs. the lowest categories of fat or fatty acids intake, we found that higher dietary trans fatty acids (TFA) intake was associated with increased risk of CVDs [RR:1.14(1.08–1.21)]. However, no association was observed between total fat, monounsaturated fatty acids (MUFA), saturated fatty acids (SFA), and polyunsaturated fatty acids (PUFA), and risk of CVDs. Subgroup analysis found a cardio-protective effect of PUFA in the studies that has been followed up more than 10 years [0.95(0.91–0.99), I^2 = 62.4%]. Dose-response analysis suggested that the risk of CVDs increased 16% [1.16 (1.07–1.25), $P_{linearity}$ = 0.033] for an increment of 2% energy/day of TFA intake.

Conclusions

This current meta-analysis of cohort studies suggested that total fat, SFA, MUFA, and PUFA intake were not associated with the risk of cardiovascular disease. However, we found that higher TFA intake is associated with greater risk of CVDs in a dose-response fashion. Furthermore, the subgroup analysis found a cardio-protective effect of PUFA in studies followed up for more than 10 years.

Comment

Cardiovascular disease is still the leading cause of death globally. Diet is seen as being the leading contributor to this, along with other lifestyle factors such as exercise, and we are increasingly aware of the roles of stress and mental health, and negative changes to sleeping patterns. Critical to the debate around cardiovascular disease and diet is the topic of saturated fat and whether or not it has a major role to play in the incidence and severity of heart disease and to all-cause mortality. As previously

mentioned in this issue of The Carb-Appropriate Research Review, the evidence overall does not suggest any strong link between saturated fat and either all-cause or cardiovascular disease mortality and yet, the reduction of saturated fat is still universally recommended. Much of this recommendation relies on substitution data, especially from the Hooper analysis[41] which has also recently fallen under some debate due to a reanalysis of the data using different (and probably more appropriate) statistical methods which showed no effect of limiting saturated fat for the prevention of cardiovascular disease.[42]

In this paper, Zhu and colleagues appraised over 100,000 papers for inclusion and finally analysed 43 publications to determine the effect of saturated fat on cardiovascular mortality outcomes. Some of the key findings included:

- No effect on cardiovascular risk from total fat intake (RR 0.97; 95% CI, 0.93–1.01)
- No effect of highest vs lowest intakes of saturated fat on cardiovascular risk (RR 0.97; 95% CI, 0.93–1.02)
- No influence of monounsaturated fat on cardiovascular disease risk (RR 0.97; 95% CI, 0.93–1.01)
- No effect of highest vs lowest intakes of polyunsaturated fats on cardiovascular disease risk (RR 0.97; 95% CI, 0.93–1.004)
- Highest vs lowest intakes of trans-fatty acids *were* associated with increased risk of cardiovascular disease (RR 1.14; 95% CI, 1.08–1.21)

Was there an effect of the 'dose' of these fats?

Dose-response analysis didn't yield significant results and the results were also conflicting. Trends were observed for reduced risk with increased fat intake overall, increased saturated fat (to around 30% of calories), monounsaturated fat, with reduced risk from baseline for increased % of calories from polyunsaturated fats, and worsened risk with increased intakes of trans-fats.

However, when absolute intakes (i.e. grams per day) were analysed the results are even less clear as you can see in the graphs below.

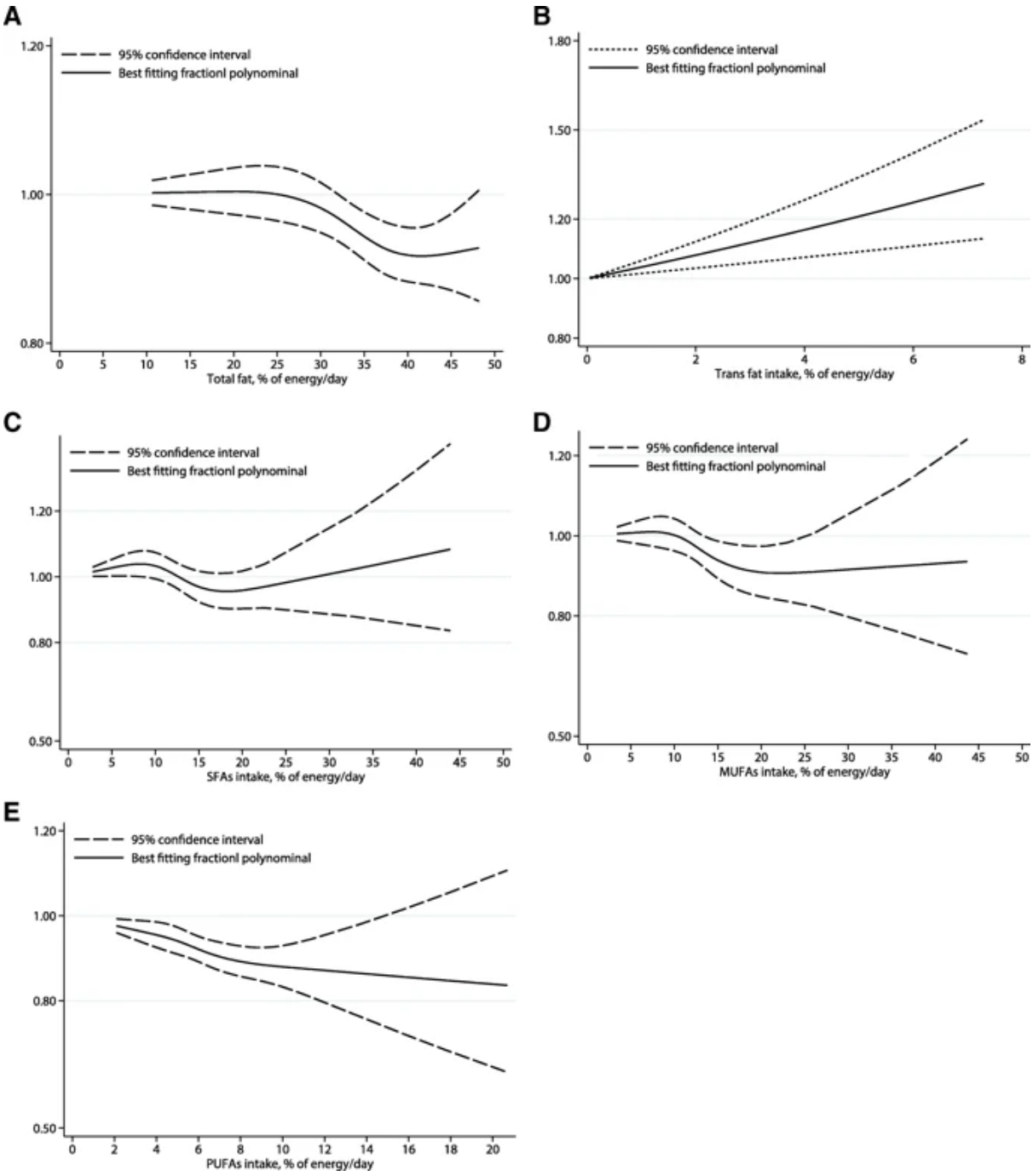

Figure 4. Dose-response analyses of the linear association between dietary total fat (a), trans-fatty acids (b), saturated fatty acids (c), monounsaturated fatty acids (d), and polyunsaturated fatty acids intake (e) and the risk of cardiovascular disease

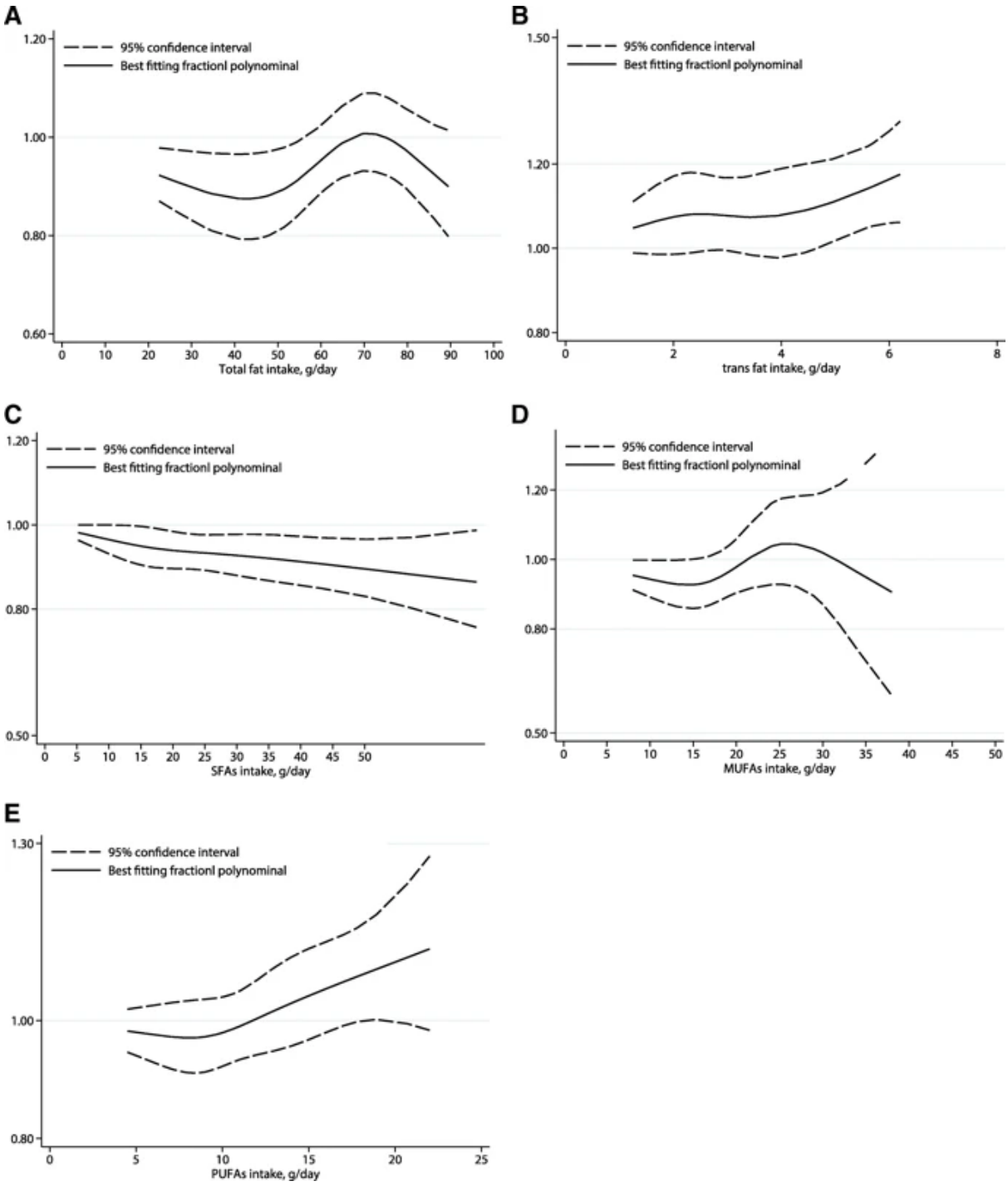

Figure 5. Dose-response analyses of the linear association between dietary total fat (a), trans-fatty acids (b), saturated fatty acids (c), monounsaturated fatty acids (d), and polyunsaturated fatty acids intake (e) and the risk of cardiovascular disease(g/d)

What does this tell us overall?

This study is consistent with the existing research. While some studies show a very small potential risk from saturated fats, others show no association or even benefit. But the overall effect size is very small and when we consider all the other factors at play, is so small as to be 'statistical noise'. In this particular study this is shown, with small effect sizes that cross over the 'risk line' of 1.0 (meaning that we can't be sure whether they benefit, harm) leaving us to conclude that they probably have no effect whatsoever.

This is true not just for saturated fats, but for ***all fat types!...*** And indeed, for fat intake overall. The only fat to show harm is trans-fat and even that has a fairly modest effect. Not that I suggest people eat trans-fats! BUT the harm from inadvertently ingesting some trans-fats is likely to be very small indeed and of course, some naturally occurring trans-fats are likely to be health-promoting (like vaccenic acid from meat and dairy for example).

Overall, the take-home message is that your overall fat intake, or the type of fat that you consume, is not likely to be a significant modifier of your future health. The key priority should be, that the fats, and the foods overall that you consume, are mostly natural, whole, and unprocessed wherever possible.

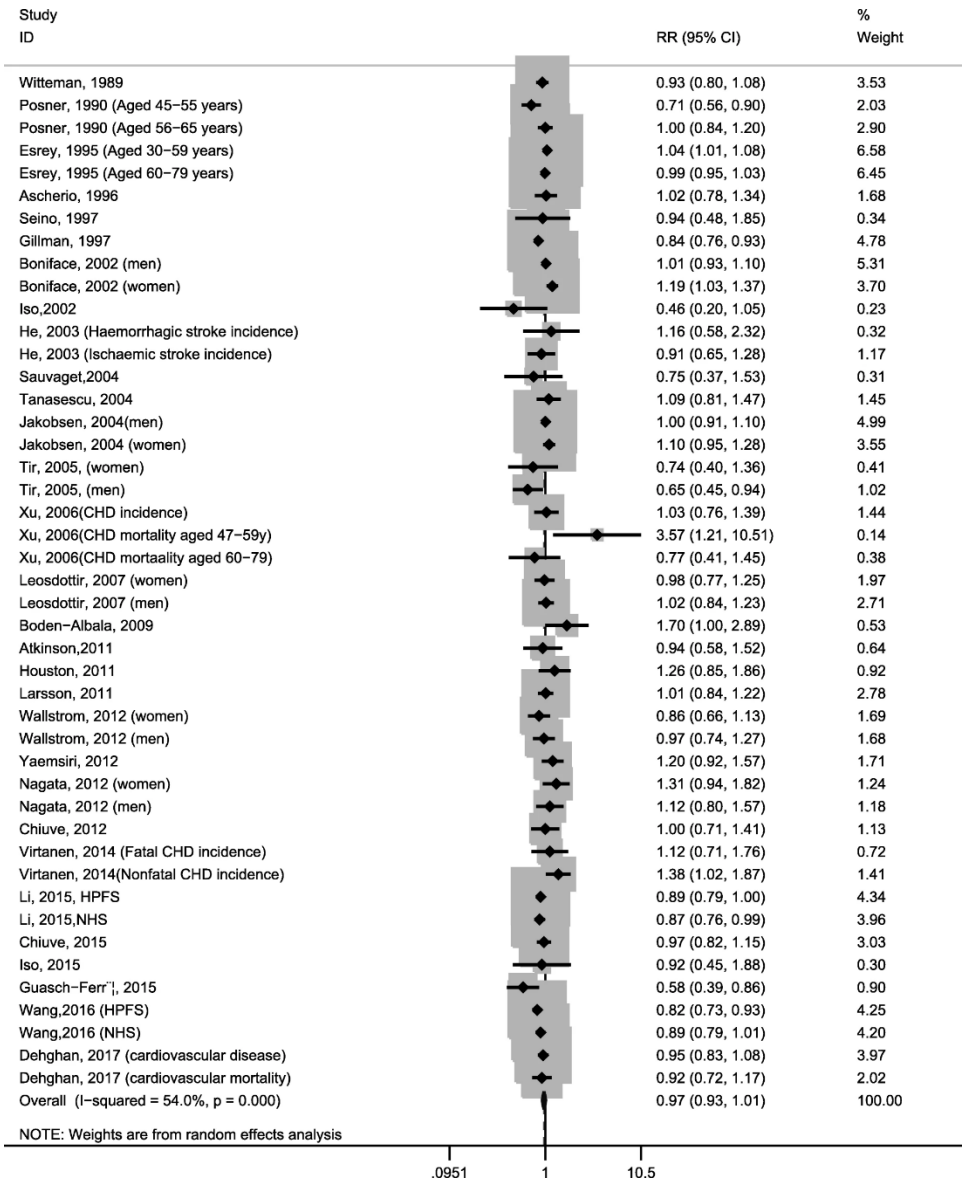

Figure 6. Plot showing the risk ratios of overall fat intake on cardiovascular disease from included studies.

IN THE MEDIA

The big fat debate over whether keto-style diets are right for reversing type 2 diabetes

John McCrone

Stuff News | August 19, 2019

https://www.stuff.co.nz/national/health/115019433/the-big-fat-debate-over-whether-ketostyle-diets-are-right-for-reversing-diabetes?

Article Summary

"If a low carbohydrate diet could reverse type 2 diabetes, you would think experts would be rushing to recommend it. So why the caution?"

In this article, the case of Taupō GP Dr Glen Davies is highlighted. Dr Davies has been applying a low-carb dietary approach to treat type 2 diabetes for several years. The approach has led to the remission of diabetes and metabolic syndrome for many of his patients. However, the medical community and many in the research community are yet to embrace low-carb nutrition as a component of the treatment of metabolic disorder and diabetes.

Since the 1970s we have eaten more overall and we eat more ultra-refined and processed foods and this has led to an increase in the prevalence of diabetes, metabolic syndrome (pre-diabetes) and obesity.

Researchers like Otago University's Professor Jim Mann have consistently criticised ketogenic diets due to the perceived dangers of saturated fat typically found in higher quantities in lower-carb and consequently higher-fat diets. He suggests that people should derive half of their calories from carbohydrate. On the other hand, Professor Grant Schofield of AUT takes a contrary position. He highlights that almost all the current research shows little to no danger from saturated fat.

Comment

In my humble opinion... (but what would I know, I'm only one of a handful of people who have actually completed their doctorates specifically in ketogenic diets!) low-carb approaches are the single best intervention for those with diabetes. To ignore this is to blatantly disregard the evidence for low-carb in relation to metabolic syndrome overall.

What's best for treating diabetes?

While many diets including the Mediterranean diet,[43-46] and vegan and vegetarian diets[47] can improve blood sugar control and help to reduce the risk of developing diabetes (in fact, ANY diet that is based on natural, unrefined foods is likely to help you avoid diabetes), the research is

also clear that low-carb diets are the most effective for *treating* diabetes.

> the research is clear that low-carb diets are the most effective for *treating* diabetes

Low-carbohydrate diets significantly reduce blood glucose levels and improve glucose control.[48] They also consistently improve the most important cardiometabolic risk factors such as triglycerides and HDL cholesterol, more than standard-care, or higher-carbohydrate diets,[49] which stands in contrast to the claims of cardiovascular risk from these diets (and remember that those with insulin resistance adhere better to carbohydrate restricted diets).[27] Overall, low-carbohydrate and ketogenic diets are more effective than other dietary interventions for the treatment and management of diabetes with an approximately 150% greater reduction in HbA1c (a measure of average blood glucose levels) as a result of low-carb diets.[50]

...but should we be worried about saturated fat in low-carb diets?

There is an almost complete lack of any strong evidence that saturated fat worsens cardiovascular (heart and vascular) health. I have reviewed aspects of this evidence in previous articles and issues of *CARR* and almost all reviews of the scientific evidence find little or no association between saturated fat intake and CVD mortality.[51-53] For example, a Cochrane review of randomised studies of the effect of modified or reduced fat interventions on total and cardiovascular disease (CVD) mortality by Hooper and colleagues showed no overall effect of the diets on either outcome (total mortality: relative risk 0.98, 95% CI: 0.93 to 1.04; and for CVD mortality: relative risk: 0.94, 95% CI 0.85 to 1.04).[54] That notwithstanding, *some* few people might experience significant worsening of LDL cholesterol when on a low-carb diet that is significantly high in saturated fat. I have found in clinical practice (assuming a low-carb diet is actually indicated for the client) that a simple substitution of some higher saturated fat oils (like butter and coconut oil) for unsaturated oils like olive, flax, and hemp, addresses this rapidly.

What about fibre?

In the article above, Professor Mann makes the point that high 'high carb' diet is mostly necessary to address getting enough fibre. However, one does not need to be higher carb in order to get enough fibre and gut-supporting resistant starches. In fact, in my experience, often when people are attempting to follow standard dietary guidelines, they end up eating relatively low amounts of fibre, especially in relation to their overall carbohydrate intake, because they are eating a lot of low-fat, high-carb, refined foods that are listed as 'heart healthy' options (i.e. 'heart tick' foods). A lower-carb diet that includes plenty of veggies contain plenty of fibre and this has been demonstrated in research led by my colleague Dr Caryn Zinn, in which their healthy, low-carbohydrate diet exceeded recommended fibre intakes by 50%.[55]

Research by Dr Caryn Zinn has shown that a healthy, low-carbohydrate diet exceeded recommended fibre intakes by 50%

The take-home messages from the evidence are that:

- Low-carb diets are the most effective for the treatment of diabetes
- Those with existing metabolic syndrome are likely to adhere to low-carb better
- Saturated fat intake is not of major concern in a low-carb diet
- Low-carb diets based on healthy, unrefined foods contain more than the recommended intake of fibre
- Diabetes risk can be lessened through any diet that is based on natural and unprocessed foods

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