

Ketogenic Diet

There is no scientific proof of the superiority, safety and sustainability of the ketogenic diet

- The main thrust of the keto campaign rests on the tenet that

“carbohydrates are noxious to the health of the population”

- the low-fat diets advocated by professional associations for decades have induced the current epidemic of obesity and diabetes mellitus.

Banting wrote in his letter on Corpulence

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“to abstain as much as possible [from] ... bread, butter, milk, sugar, beer and potatoes.”

- In adherence with such a diet he lost 2–3.5 pounds per week and became a slim 165-pound man from his corpulent 202 pounds just a few months earlier.

- Later in the letter he describes a typical breakfast in his new diet and states:

“For breakfast, I take four or five ounces of beef, mouton, kidneys, broiled fish, bacon or cold meats of any kind except pork, a large cup of tea without milk or sugar and a small biscuit ...”

- Banting introduced the notion that obesity is a chronic ailment and proposed a ketogenic approach to weight loss long before we even started talking about it!

Conti..

- But toward the end Banting warns the reader of another important fact:

“I am now in that happy, comfortable state, that I should not hesitate to indulge in any fancy in regard to diet, but if I did so, should watch the consequences, and not continue any course which might add to weight or bulk and consequent discomfort.”

- That is to say, weight loss is to be preserved and the effectiveness of any diet is to be measured in the potential for maintenance.

So, here are a few facts no one may be able to dispute:

1. Restricting calories of any type induces weight loss;
2. A diet rich in fats and proteins causes early satiety therefore a reduction in ingestion of calories;
3. Limiting or eliminating carbohydrates is a major contributor to weight loss;
4. Introducing a keto diet mostly, or almost exclusively, based on animal products induces rapid weight loss.

Weight loss and its sustainability

- Keto can induce a rapid & gratifying weight loss but, like any other diet, it must be sustained to keep weight off.
- The studies completed so far have been very short
- Not convincingly demonstrate that the keto diet is more sustainable and that the effects are more durable than those of others.

Weight loss and its sustainability

- In a metanalysis comparing low-fat vs low-carbohydrate diets, Bueno et al. reviewed 9 studies of 12-month duration and 4 additional studies lasting 24 months.
- They concluded that keto provided on average
 - 0.9 kg additional weight loss compared to low-fat diets,
 - Along with a significant reduction in triglycerides, and
 - Diastolic blood pressure,
 - In the face of a significant increase in HDL-c and LDL-c.
- These results are encouraging but have small sample size (60–200 patients, with one study including 305 patients),
- There was no report on the long-term outcome of the enrolled subjects.

Weight loss and its sustainability

- Hall et al. study with 17 overweight or obese subjects
- to isocaloric low-fat vs low-carbohydrate.
- The energy loss (in Kcal per day) induced by the two diets was not different.
- Although keto induced a substantial decrease in insulin secretion along with increasing circulating free-fatty acids and ketones, it did not induce a greater body fat loss than the low fat diet.
- It is important to remember that a strict keto diet includes no more than 10% of the total daily calorie intake in the form of carbohydrates, 20% as proteins and the remaining as fats.

Problems with sustainability

- Halitosis,
- Constipation and diarrhea,
- Muscle cramps,
- Headaches,
- Unpalatability
- Vitamin deficiencies,
- Nephrolithiasis

and other side effects may also deter many patients from persevering on the keto diet.

Raise in LDL-c

- It is worrisome that virtually every study involving keto demonstrates a significant increase in LDL-c.
- Healthy, normal weight volunteers exposed to a 3-week long keto diet demonstrated:
 - 44% increase in serum LDL-c
 - 30% reduction in the expression of the LDL-c receptor on the surface of peripheral blood mononuclear cells.

Raise in LDL-c

- In a pediatric study, 141 children with intractable seizure disorder were treated with the keto diet and strictly monitored for development of a ketogenic state.
- Total cholesterol, LDL, VLDL, non-HDL cholesterol, triglycerides and total apoB increased significantly while the HDL level decreased significantly after 6 months of treatment.
- Although attenuated, a significant increase in all apoB containing lipoproteins persisted at 12 and 24 months from treatment inception.

LDL particle size

- A very-low carbohydrate, high fat diet increases the number of large buoyant LDL particles but not that of the noxious small-dense LDL particles.
- However, several issues should be remarked upon:
 - First, the total apoB concentration increases and independent of any other consideration
 - LDL is the cause of atherosclerosis, and none of the international guidelines on risk reduction differentiates between large and small LDL particle size.
- This is likely due to the weak and conflicting evidence that LDL particle size matters more than LDL mass.
- Importantly, the number of particles and the serum level of apoB containing lipoproteins have been clearly shown to increase cardiovascular risk, not the size of the LDL particles.

LDL particle size

- In a sub-study of the Multi-Ethnic Study of Atherosclerosis (MESA):
- small and large LDL particles were equally associated with increased carotid intima media thickness.
- Ultimately, the number of apoB containing lipoproteins circulating in the arterial lumen will determine the
 - Number of particles infiltrating the arterial wall and
 - The number of particles retained in the subintimal space, where they will promote atherosclerosis plaque growth.
- Paradoxically, small dense LDL may even protect against repeat cardiovascular events.

Plant vs Animal diet

- Two recent long-term prospective observational studies reported on the comparison of plant-based vs animal-based diets.
 - **Animal protein intake was not associated with increased all-cause mortality** but was associated with a significant increase in cardiovascular mortality
 - On the contrary, **plant-based diets were associated with a significant reduction in all-cause and cardiovascular mortality**

Plant vs Animal diet

- A switch from an animal to a plant-based diet was associated with a 34% reduction in all-cause mortality
- A more recent Japanese study confirmed and reinforced the above findings.
- Among 70,696 adults over a 20-year follow-up period after collecting food frequency questionnaires to assess plant vs animal-based protein intake between 1995 and 1999.
- Again, animal protein intake was not associated with total or cause specific mortality.

Is There a Yo-Yo Effect?

- Many studies demonstrate that a ketogenic diet, at least in the short-term, results in greater weight loss than low-fat diets from a long term perspective the success of a nutritional approach is defined by the amount of weight regain.
- From this point of view, fewer data are available, in particular regarding so-called weight cycling or yo-yo effect.
- Some opponents and doubters of Keto suggest that any beneficial effects are only transient.
- There is no universally accepted definition of “successful weight loss maintenance” following a diet
- Wing and Hill in 2001, defined it as “individuals who have intentionally lost at least 10% of their body weight and kept it off at least one year”.

Is There a Yo-Yo Effect?

- Both extremely high (60% and above) and low carbohydrate diets (<30% carbs) were shown to have higher mortality rates.
- The risk of dying was lowest when the carbohydrate intake was between 50 and 55 per cent.

Low carbohydrate/high protein

- Noto and colleagues suggested a possible harmful effect of low carbohydrate/high protein diet (LC/HP) on health:
- *i.e.*, an increase of all-cause mortality risk whilst there was no effect on CVD mortality.
- There is evidence showing that short-term Keto impair bone mass density;
- In children with intractable epilepsy may lead to a progressive reduction of bone mineral content .

Hypertensive effect

- Susceptible to the hypertensive effect of amino acids, especially of the sulphated variety.
 - Subjects with renal insufficiency,
 - Kidney transplant patients and
 - People with metabolic syndrome or
 - Other obesity-related conditions, will be more

Relation with Carbohydrates

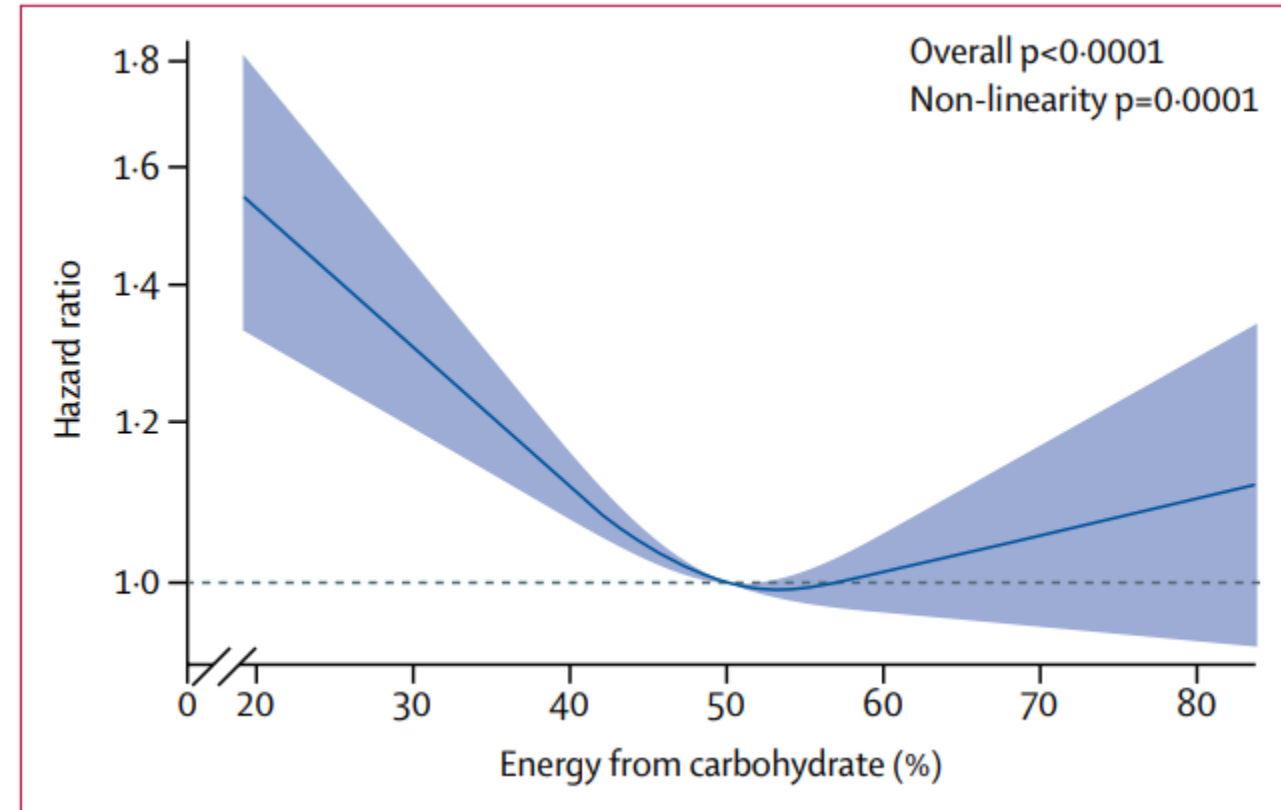
A recent study on dietary carbohydrate and mortality, seidelmann *et al.*
showed that there existed a u-shaped relationship
Between carbohydrate intake and mortality.

Relation with Carbohydrates

U-shaped association between percentage of energy from carbohydrate and all-cause mortality in the ARIC cohort. The reference level is 50% energy from carbohydrate.

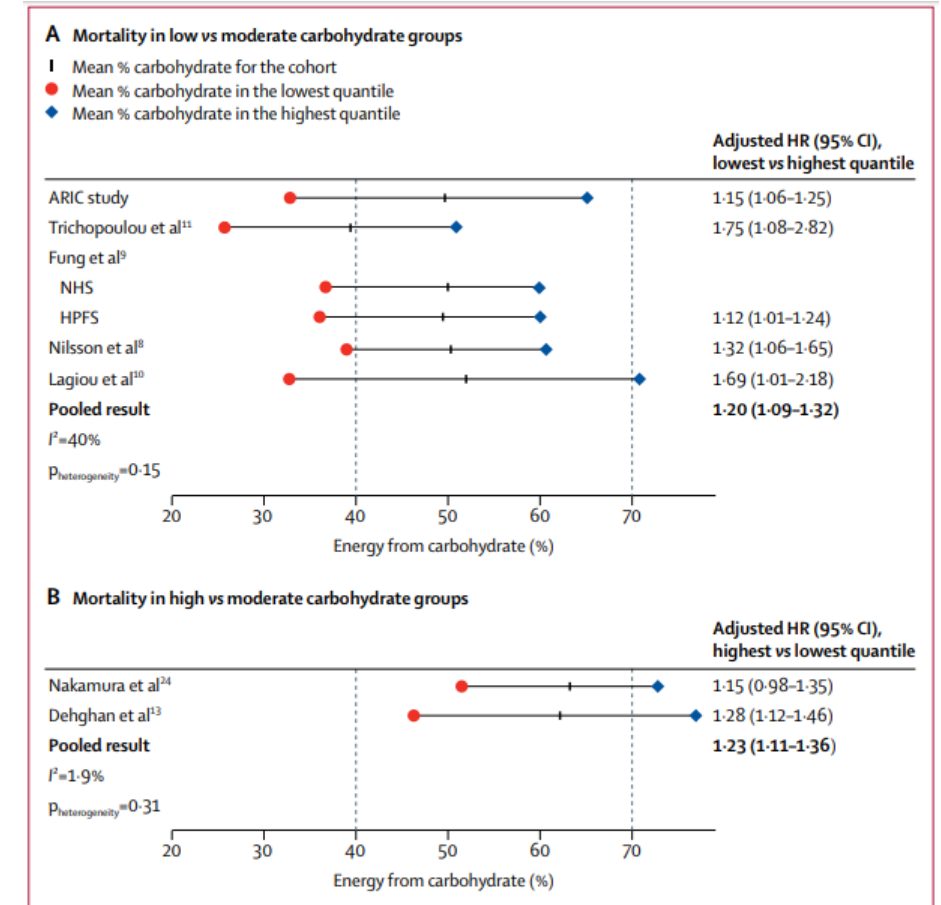
ARIC=Atherosclerosis Risk in Communities

Seidelmann SB et al. Lancet Public Health 2018; 3: e419–28



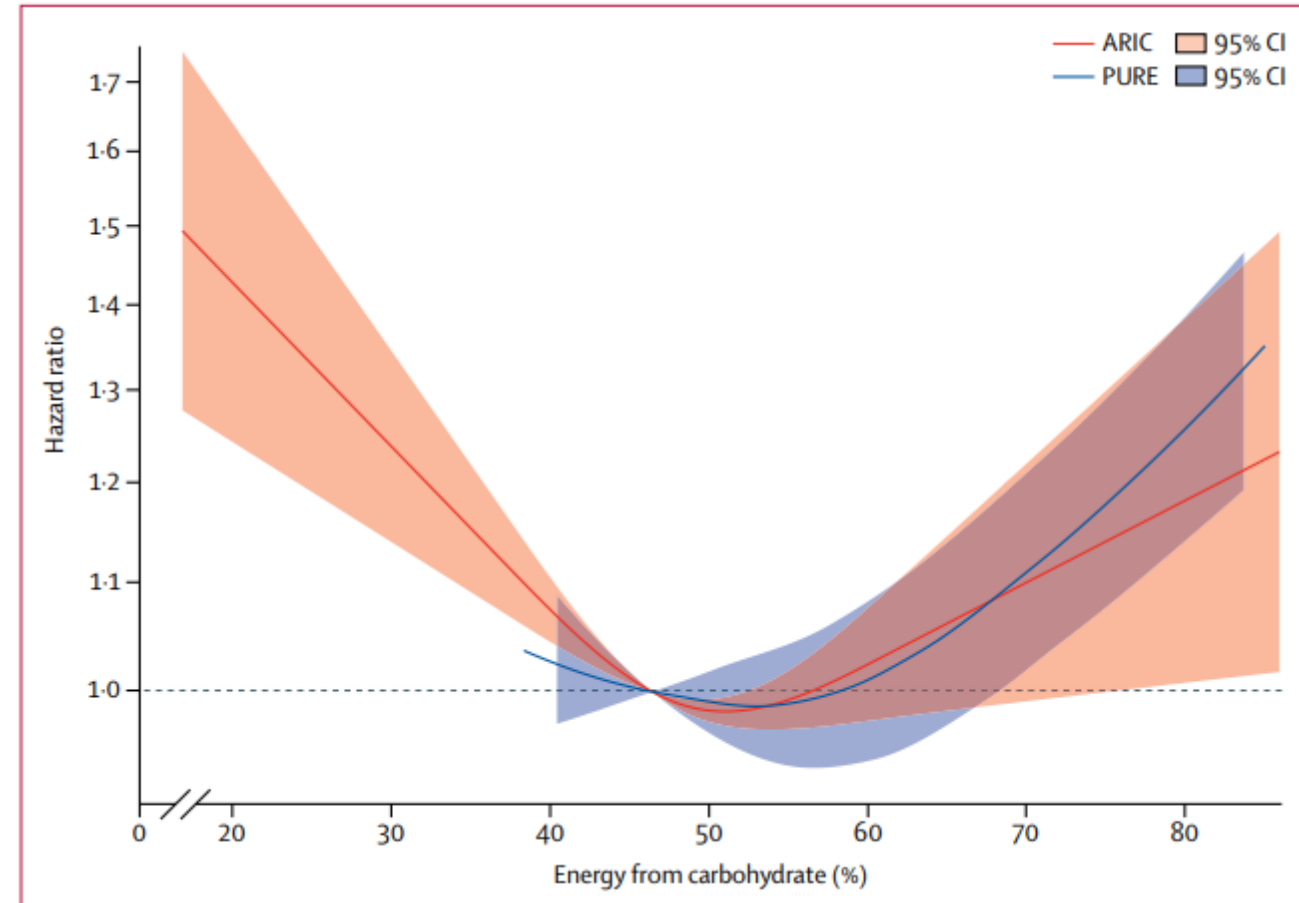
Relation with Carbohydrates

- Significantly increased risk of all-cause mortality among participants with low carbohydrate versus moderate carbohydrate consumption
- Carbohydrate intake and mortality risk across multiple cohort studies



Relation with Carbohydrates

- U-shaped association between percentage of energy from carbohydrate and all-cause mortality in the ARIC and PURE cohort studies
- Overlapping and continuous relationship between percentage of energy from carbohydrate intake and mortality in these cohorts.

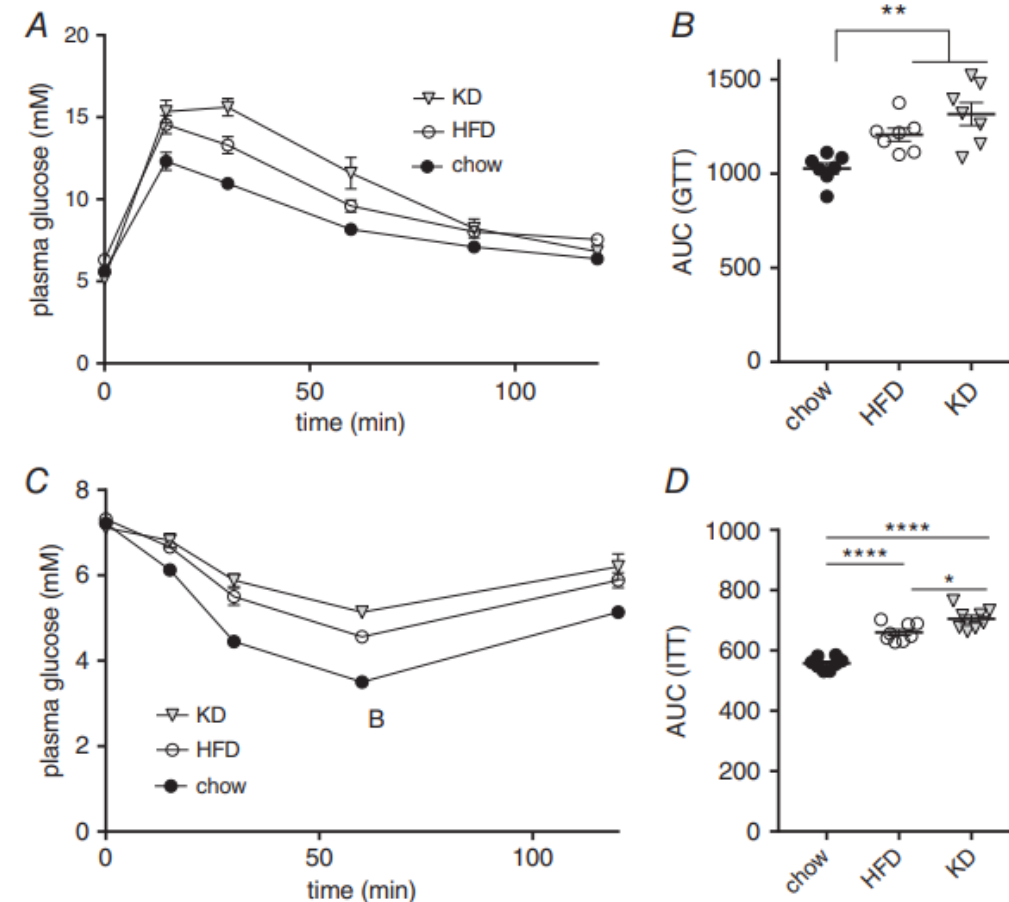


Short-term KD or HFD feeding causes impaired glucose clearance and insulin tolerance

- A, I.P. GTT of mice fed chow, KD or HFD for 3 days, after a 6 h fast.
- B, AUC of GTT.
- C, I.P. ITT of mice fed chow, KD or HFD for 3 days, after a 6 h fast.
- D, AUC of ITT (n = 7–8). Data are plotted as the mean $\pm$ SEM.

*P < 0.05, **P < 0.01, ****P < 0.0001 by ANOVA.

KD = Keto diet
HFD = High fat diet



Biases in studies

- Observations from a study often quoted as demonstrating the superiority of keto compared to low fat diets in reducing hemoglobin A1c and inducing weight loss in patients with diabetes mellitus type 2:
- It was an open labelled non-randomized study
- during which patients were exposed to 1-year of a continuous care intervention or usual care [25].
- “Intervention arm” (i.e. keto diet), received extensive counseling and tools to measure their adherence to the diet as well as their progress.

Biases in studies

- These included:
 - a cellular-connected body weight scale,
 - a finger-stick blood glucose and ketone meter,
 - a blood pressure cuff,
 - access to a web-based application for biomarker reporting and monitoring,
 - education, and communication with a remote care team consisting of a health coach,
 - a medical provider and social support via an online peer community.
- The patients who volunteered to adhere to usual care simply continued to see their family doctors and received advice on diet.
- One can hardly imagine this to be a balanced trial and fair a comparison.

Safety and long-term benefits

- Despite the well-advertised weight loss and the reduction in insulin requirements and hemoglobin A1c, the long-term benefits of keto have not been demonstrated.

High-Protein Diet-Induced Satiety

- When high-protein menus are offered to subjects at each meal for a duration of one to several days, the metabolic reactions of a high-protein diet are established (49, 97, 107, 108).
- In several studies of high-protein diets in normal weight healthy subjects, a continuously higher satiety was shown throughout the day after consumption of the high-protein diet in comparison with the normal-protein diet including in the energy-balance-controlled environment of a respiration chamber (49, 97, 107, 108).
- Here, a normal-protein diet given in energy balance contains 10% to 15% of energy from protein (107), and a high-protein diet in energy balance contains 20% to 30% of energy from protein (107).

High-Protein Diet-Induced Satiety

- A high-protein diet in the presence of carbohydrate stimulates GLP-1 release (49, 108), which triggers insulin release.
- More importantly, only high-protein diet-induced satiety is primarily related to elevated energy expenditure (49, 97, 107, 108), which implies that oxygen consumption and body temperature increase, leading to a feeling of being deprived of oxygen and thus promoting satiety (97, 107).

So what is the final message?

- One of the challenges of low-carbohydrate diets is that these have
 - A lower intake of vegetables, fruits and grains and
 - Increased intakes of fat which can be detrimental.
- Long-term low-carbohydrate diets with increased fat consumption have been hypothesized to stimulate
 - Inflammatory pathways,
 - Oxidative stress and
 - Promote biological ageing.

So what is the final message?

- The biggest problem with extreme diets like keto diets is their sustainability.
- People are initially thrilled with the weight loss and the excellent diabetes control they get, after using keto diets.
- Slowly, however, they get bored with the diet.
- Furthermore, many feel weak and frustrated and start increasing the carbohydrate intake, and soon they are back to their original weight and diabetes control.
- Recent studies also suggest that ketogenic diets may, in fact, induce hepatic insulin resistance.
- There are also reports of micronutrient deficiency and cardiovascular safety.
- Hence, many more studies need to be done before these diets are widely recommended.

Take home message

- The dictum, 'Moderation is the key' should be used, while following any long-term diet plan.
- While low-carbohydrate ketogenic diet does, admittedly, show dramatic improvements in the short term, these can increase morbidity and mortality in the long run and are rarely sustainable.
- Instead of letting the pendulum of nutrients swing on either side, one must be vigilant of the balance and interplay of nutrients, and there should be a representation of all food groups on the plate¹⁸.

Take home message

- For Indians, it appears that it would be most prudent to have a diet with about 50 per cent carbohydrate (using complex carbs and whole grains such as brown rice or whole wheat)
- About 20-25 per cent protein (preferably from vegetable proteins such as legumes and pulses) and the remaining 25-30 per cent from healthy fats like monounsaturated fats (*e.g.* groundnut oil or mustard oil and nuts and seeds) along with plenty of green leafy vegetables.
- Such a diet may not immediately give dramatic results as far as weight reduction is concerned.
- However, it will be sustainable in the long term and will be less risky and certainly more healthy and also help prevent non-communicable diseases such as diabetes, cardiovascular disease and certain cancers.

Thank you