Workshop Report

UK Food Standards Agency Workshop Report: Carbohydrate and Cardiovascular Risk

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This report summarises a workshop convened by the UK Food Standards Agency (FSA) on 14 October 2008 to discuss current FSA funded research on carbohydrate and cardiovascular health. The objective of this workshop was to discuss the results of recent research and to identify any areas which could inform future FSA research calls. This workshop highlighted that the FSA is currently funding some of the largest, well-powered intervention trials investigating the type of fat and carbohydrate, whole grains and fruit and vegetables, on various CVD risk factors. Results of these trials will make a substantive contribution to the evidence on diet and cardiovascular risk.

The UK Food Standards Agency (FSA) convened a workshop on 14 October 2008 chaired by Professor Philip Calder to discuss current FSA funded research on carbohydrate and cardiovascular health commissioned under its N02 Diet and Cardiovascular Disease research programme. In particular the workshop focused on research from ongoing and recently completed dietary intervention studies investigating the impact of the type of carbohydrate and fat, whole grains, and fruit and vegetables, on cardiovascular disease (CVD) risk. The aim of the workshop was to discuss the results and implications of this research and to identify any areas which could inform future FSA research calls.

Dr John Stanley, N02 Programme Advisor, presented an overview of the evidence surrounding the three areas: type of carbohydrate and fat; wholegrain; and fruit and vegetables, on CVD risk. This overview was followed by project specific presentations by Dr Susan Jebb, Dr Frank Thies, Professor Chris Seal, Dr Damian McCall and Professor Tom Sanders. The presentations were followed by a general discussion of the scientific issues raised during the presentations.
Background

Cardiovascular health

Cardiovascular disease is the leading cause of death world-wide and the World Health Organisation (WHO) suggests one-third of all global deaths (15.3 million) are caused by CVD. In the UK CVD is one of the main causes of premature death, attributing to 30% and 22% of premature deaths in men and women respectively. In 2006, CVD accounted for 197,767 deaths or 35% of all deaths, of which 94,381 were from coronary heart disease (CHD) and 55,098 deaths from stroke. About 851,000 people in the UK have had a heart attack and over 1.1 million suffer from angina. In addition, about 707,000 people have definite heart failure.

The burden of CVD is a major public health concern, and there is convincing evidence that dietary and nutritional factors can reduce risk. In working towards its key strategic aim to reduce diet-related disease, the FSA commissions research into diet, nutrition and CVD risk under its N02 Diet and Cardiovascular Disease research programme.

The aim of this programme is to provide sound scientific evidence on the biological effects of dietary components on cardiovascular health which can be used in the formulation of healthy eating recommendations for consumers. The scientific and technical objectives of the programme focus on long term intervention studies in free living humans examining the effects of modifying diet (e.g. increasing fruit and vegetable intake) on cardiovascular health, with the maintenance of cardiovascular health and the prevention of CVD as the main focus.

Measurement of cardiovascular disease

The measurement of CVD itself is not a practical endpoint for most intervention trials. In current FSA trials, CVD risk factors tend to be used as endpoints. In addition to traditional, well-established risk factors such as dyslipidaemia, insulin resistance and hypertension, an earlier FSA workshop recommended that measures of endothelial function may provide a useful non-invasive methodology for assessing a clinically relevant surrogate endpoint. Taking this recommendation into account the FSA is moving towards commissioning further research using novel measures of vascular function and continuing its work on insulin resistance where the impact of dietary modification is less well characterised than for dyslipidaemia or hypertension.

Dietary fat, carbohydrate and cardiovascular disease

Current dietary recommendations advise the consumption of no more than 10% of dietary energy from saturated fat; however current intakes in the UK population average 13%. There is evidence to suggest that a diet high in saturated fat (SFA) increases the blood concentration of total cholesterol particularly low density lipoprotein (LDL) cholesterol in the bloodstream, which is strongly associated with risk of CVD. On the other hand, replacing fat with carbohydrate decreases HDL cholesterol, which is associated with increased risk of CVD. However, cross-sectional studies have suggested that the HDL lowering effect of carbohydrate may be influenced by the glycemic index of the diet. The Prospective Triallist
Collaboration concluded that the ratio of total:HDL cholesterol was twice as informative of CVD risk than total cholesterol. A central issue in public health nutrition is to determine the optimal quantity and composition of both fat and carbohydrate in the diet to reduce the risk of CVD.

A review by McAuley and Mann assessed several intervention trials comparing the effects of saturated and unsaturated fat on insulin sensitivity in healthy individuals and type 2 diabetics. Results from these trials were inconclusive, with many being underpowered and of a short duration.

To date the largest published trial investigating the effect of type of dietary fat on insulin sensitivity is the KANWU study. One hundred and sixty two subjects were randomised to either a high SFA or high monounsaturated fat (MUFA) diet. Insulin sensitivity measured by intravenous glucose tolerance test (IVGTT) was significantly lowered by the high SFA diet but not by the MUFA diet. A post-hoc analysis suggested that this effect of MUFA only occurred in the subjects that consumed a total fat below <37% of energy.

In another randomised cross-over trial 59 subjects followed a SFA rich diet for 28 days and were then randomised to a low fat, high carbohydrate diet or a high MUFA diet (‘Mediterranean diet’) for 28 days in each group. Both diets demonstrated an improvement in insulin sensitivity compared to a diet higher in saturated fat.

A number of trials have also investigated percentage and type of fat and carbohydrate on measurements of vascular function. Perez-Jimenez et al. reported a high MUFA diet decreased plasma von Willebrand Factor (vWF), tissue factor pathway inhibitor (TFPI) and plasminogen activator inhibitor -1(PAI-1) in 25 healthy male subjects. Similarly Fuentes et al. observed an improvement in vascular function measured by flow mediated dilation (FMD) in 22 hypercholesterolaemic men consuming a high MUFA diet. Keogh et al. also reported that a high SFA diet resulted in significant deterioration in FMD of the brachial artery compared to the high PUFA, MUFA or carbohydrate diets. In comparison, Ashton et al. observed no effect of a modified fat (with a high MUFA content) or a low fat, high carbohydrate diet on arterial elasticity in 28 healthy subjects. No effect on FMD of the brachial artery was observed in a randomised cross over trial of 32 healthy subjects consuming a low fat diet.

The majority of studies have been short in duration, conducted in a small number of subjects, and have been statistically underpowered. In 2003, the FSA commissioned a large multi-centre trial to investigate the impact of the amount and type of dietary fat and carbohydrate (CHO) on metabolic syndrome.

**N02031 – Impact of the amount and type of dietary fat and carbohydrate on metabolic syndrome (RISCK study)**

Dr Susan Jebb presented on the large FSA funded multi-centre randomised controlled parallel study investigating the impact of the amount and type of dietary fat and CHO on metabolic syndrome.

The main aim of the RISCK (University of Reading, Imperial College, University of Surrey, MRC Human Nutrition Research, Cambridge and Kings College London)
The study was to identify and recruit subjects predisposed to the development of the metabolic syndrome; to develop a strategy to attain five isoenergetic dietary groups differing only in the amount and composition of dietary fat and carbohydrate; and to test the impact of these changes in dietary composition on CVD risk factors associated with metabolic syndrome, especially insulin sensitivity.

Using a combination of existing guidelines for identification of the metabolic syndrome and clinical cut-offs associated with increased risk of CVD, a screening tool was developed to identify and recruit subjects at risk of the metabolic syndrome.

The five isoenergetic dietary intervention groups developed for this study were:

- the reference diet – high SFA/high glycemic index (38% energy from fat, 18% energy from SFA, 12% energy from MUFA, 6% energy from PUFA and 45% energy from CHO);
- high MUFA, high GI diet (38% energy from fat, 10% energy from SFA, 20% energy from MUFA, 6% from PUFA and 45% from CHO);
- high MUFA, low GI diet (38% energy from fat, 10% energy from SFA, 20% energy from MUFA, 6% from PUFA and 45% from CHO);
- low fat, high GI diet (28% energy from fat, 10% energy from SFA, 12% energy from MUFA, 6% energy from PUFA and 45% energy from CHO);
- low fat, low GI diet (28% energy from fat, 10% energy from SFA, 12% energy from MUFA, 6% energy from PUFA and 55% energy from CHO).

To achieve the fat and CHO modification, sources of fat and CHO were replaced with study foods specifically developed with relevant fatty acid profile and CHO content.\(^1^8\)

Subjects completed a 4 week run in phase where the reference diet was consumed prior to being randomised to one of the five dietary groups for a further 24 weeks. In total 720 subjects were recruited with 548 successfully completing the trial. Almost a quarter of subjects did not complete the study, primarily due to the demands associated with making extensive changes to their dietary patterns. Most dropouts occurred during the run-in phase prior to the main intervention period.

The study was powered to measure the primary outcome measure insulin resistance, which was measured by reduced sampling IVGTT protocol, secondary outcome measures included many CVD risk markers, including blood lipid profiles, blood pressure, inflammatory markers and markers of endothelial function. Compliance was measured through diet diaries and analysis of plasma fatty acids. Further details of the study design have been previously published.\(^1^9\)

The screening tool successfully identified participants predisposed to CVD. The dietary targets for each diet were generally met and changes in plasma phospholipid fatty acids confirmed compliance. Overall no significant impact of high MUFA, low fat or GI on fasting or post-prandial measures of insulin sensitivity was observed. The replacement of SFA with either MUFA or CHO resulted in LDL lowering effects. There were additional reductions in total and LDL cholesterol on the low GI diets while the high MUFA diet led to a more favourable total cholesterol:HDL ratio.
This is currently one of the largest controlled dietary intervention trials and is sufficiently powered to detect effects of replacing SFA with MUFA and CHO and the effect on metabolic syndrome and CVD risk factors.

**Whole grain consumption and cardiovascular disease**

There is good epidemiological evidence demonstrating a protective effect of high consumption of whole grains against CVD risk\(^\text{20,21,22}\). A meta-analysis of 12 cohort studies\(^\text{23}\) concluded that subjects with the highest intake of whole grain had around 26% lower risk of developing CHD compared to those with the lowest intake. An update on this meta-analysis, which included 13 studies, reported a 29% reduction in CHD risk. In a recent meta-analysis of 7 prospective cohort studies\(^\text{24}\) a 21% reduction in CHD risk was reported in the high consumers of whole grain compared with the low consumers.

To date the majority of the evidence is based on observational studies and although it is compelling, there is a lack of data from large well designed intervention trials sufficiently powered to detect a causal link. One meta-analysis\(^\text{25}\) analysed 10 randomised controlled trials on wholegrain foods and effects on CHD mortality, morbidity and on risk factors for CHD. Results from this meta-analysis showed significant lowering effects on total and LDL cholesterol concentrations, however most of the trials were short term, of poor quality and insufficiently powered. In addition 8 out of the 10 studies focused on oats as the wholegrain source.

There is therefore a need for large, well designed intervention trials with sufficient power to detect an effect of whole grain on CVD risk factors. In 2004, the FSA commissioned two such trials investigating the effect of whole grain on CVD risk factors.

**N02035 – Comparison of effects of increased whole grain foods on markers of cardiovascular risk**

Dr Frank Thies presented on the FSA funded study designed to investigate the effects of increased intake of wholegrain foods on markers of CVD risk. The aims of this study were: to test the hypothesis that three servings of wholegrain foods per day have a cardio-protective role; to characterise the effects of this intervention on cardiovascular risk factors; and to compare the effects of wheat-based wholegrain foods with a mixture of wheat and oat-based wholegrain foods.

Two hundred and thirty three healthy subjects aged 40-65 years with a BMI between 25 and 35 kg/m\(^2\) were randomised into one of three intervention groups, control (refined cereal diet, avoidance of wholegrain foods); whole wheat diet (3 servings of wholegrain foods) or whole wheat and oat diet (3 servings of wholegrain foods, including oats). Prior to commencing the 12 week intervention period, subjects took part in a 4 week run in phase, where they all consumed a refined cereal diet. The subjects randomised to the wheat based whole grain or the whole wheat and oat diet replaced three servings of refined cereals with either 3 portions of wheat or wheat and oat whole grains.
The primary outcome measure of this study was total and LDL cholesterol (the study was powered on these two markers). Blood pressure, lipoprotein profile, inflammatory markers and arterial stiffness was also measured at each time point.

In total 206 subjects completed the study. Macronutrient intake did not change throughout the trial, except NSP, which increased in the whole grain intervention groups. Systolic blood pressure and pulse pressure significantly decreased in the whole grain food groups compared to the control group. Systemic markers and lipid concentrations did not differ significantly after the intervention. Systemic markers remained mostly unaffected by the interventions apart from total and LDL cholesterol concentrations which decreased slightly in the refined group.

**N02036 – Randomised controlled trial to test the impact of increased consumption of wholegrain foods on cardiovascular disease risk (the WHOLEheart study)**

Professor Chris Seal presented on the FSA funded study investigating the impact of increased consumption of wholegrain foods on CVD risk factors.

This was a multi-centre randomised controlled study, conducted in Newcastle and Cambridge. Two hundred and sixty six subjects (aged 18-65 years; BMI > 25 kg/m^2) who habitually consumed < 1.5 portions of whole grain/day were recruited across the two centres. Subjects were randomised to one of three groups: control group (no dietary intervention); 3 servings of whole grain/day for 16 weeks; or 3 servings of whole grain/day for 8 weeks followed by 6 servings of whole grain/day for 8 weeks. Wholegrain foods (e.g. brown rice, breakfast cereal, wholemeal bread etc) were provided preweighed and packaged, with labels indicating whole grain portions in each packet to aid compliance.

Whole grain-intake was assessed by food frequency questionnaire. Plasma was analysed for lipid profile (total, LDL and HDL cholesterol and triglycerides), insulin and glucose and further biochemical markers of inflammation and endothelial function. Differences between study groups were compared using a random intercepts model with time and whole grain-intake as factors. Whole grain-intake was <20g/day at baseline, and this increased as expected during the intervention for those receiving wholegrain foods. Whole grain-intake for the control group stayed at about 20g/day throughout the study and during the 12 month follow-up period. For the 3 servings group, whole grain-intake was about 70 g/day for weeks 8 and 16, and for the second intervention group whole grain-intake was 76 g/day at week 8 and 115 g/day at week 16. Despite these significant increases in whole grain-intake there were no significant changes in plasma LDL cholesterol concentrations or any of the other biomarkers of CVD risk tested. The pattern of food intake was changed with inclusion of wholegrain foods, with several beneficial changes in nutrient intakes, especially dietary fibre and many micronutrients. These data do not support the observational data for the health benefits of wholegrain foods, however, the intervention may be too short to change the lifelong disease trajectory associated with CVD in these overweight volunteers.

In addition to investigating CVD risk the WHOLEheart study was also designed to explore factors affecting acceptability, barriers and sustainability of incorporating whole grains into the diet by conducting focus groups at 1, 6 and 12 months post
intervention. These qualitative data provide a valuable insight into consumer acceptance of wholegrain foods and the factors which influence food choice at the individual and household level.

The results from these two well designed intervention trials provide compelling evidence on whether whole grains have a protective effect on cardiovascular health.

**Fruit and vegetable and cardiovascular disease**

A number of cross-sectional and prospective cohort studies have reported a significant protective effect of fruit and vegetables on CHD risk and stroke. A meta-analysis of 9 cohort studies\(^9\) reported a beneficial association between fruit and vegetable consumption and CHD risk. A more recent meta-analysis of 13 cohort studies\(^{30}\) demonstrated a 17% decrease in CHD risk from increasing fruit and vegetable consumption from less than 3 portions to more than 5 portions per day. A small, slightly significant decrease in CHD risk was also noted where intake was increased to 3-5 portions per day. A pooled analysis of 9 cohort studies showed increased fruit and vegetable intake was associated with a reduced risk of stroke\(^{31}\). Individuals who consumed more than 5 servings/day had a significantly reduced risk of stroke compared to individuals who had less than 3 servings/day. Elevated blood pressure is the major risk factor for stroke and also an important risk factor for CHD\(^32\) and it is highly plausible that the intake of fruit and vegetables may help prevent the increase in blood pressure that occurs with age.

Only a few intervention trials have examined the cardioprotective effect of fruit and vegetables. The Dietary Approach to Stop Hypertension (DASH) study of 459 subjects\(^{33}\) was an 8 week controlled feeding study that assessed the effects on blood pressure of increased fruit and vegetable consumption alone or in addition to a combination diet (rich in fruit and vegetables, low fat dairy produce and reduced amounts of saturated fat, total fat and cholesterol). The decreases in systolic/diastolic ambulatory blood pressure were 3.1/2.0 mm on the fruit and vegetable diet, 4.6/2.6 mm Hg on the combination diet compared changes of -0.2/0.1 mmg Hg on the control diet\(^{34}\). The blood pressure lowering effects of the diets were greater in those with raised blood pressure.

A six month randomised controlled trial used a brief negotiation method to encourage increased consumption of fruit and vegetables to at least 5 portions per day\(^{35}\). Subjects reported an increase in average fruit and vegetable consumption from 3.4 to 4.9 portions/day, which resulted in a decrease in systolic blood pressure by 4.0mmHg and diastolic blood pressure by 1.5mmHg in the intervention group. Another trial used healthy lifestyle prompts\(^{36}\) including a recommendation to increase fruit and vegetables and, although fruit and vegetable consumption increased, no significant effect on blood pressure was observed.

There is a lack of randomised controlled trials investigating fruit and vegetables and CVD risk factors. Large, well designed intervention trials, sufficiently powered with vascular function as a primary outcome to detect an effect of fruit and vegetables on CVD risk factors are therefore needed. Consequently the FSA has funded two large intervention trials investigating the effect of fruit and vegetable consumption on vascular function.
**N02029 – The dose dependent effects of fruit and vegetable consumption on vascular function**

Dr Damian McCall presented on the FSA funded study investigating the dose dependent effects of fruit and vegetable consumption on vascular function.

The aim of this randomised dietary intervention trial was to examine the dose-dependent effects of fruit and vegetable consumption on cardiovascular health in subjects with hypertension. One hundred and forty seven volunteers were recruited, with 117 completing the 4 week run in phase where all subjects were limited to one portion of fruit and vegetables a day. Following the run in phase, subjects were randomised to 1 of 3 intervention groups, where they consumed either 1, 3 or 6 portions/day for 8 weeks. Compliance to the dietary intervention was measured by contemporaneous 4 day food diaries and assessment of micronutrient status pre- and post-intervention. The primary outcome measure of the study was forearm blood flow responses to intra-arterial acetylcholine. In addition, central wave reflection, upper limb pulse wave velocity and circulating inflammatory markers were measured.

Participants in the 1, 3 and 6 portions/day groups reported consuming on average 1.1, 3.2 and 5.6 portions of fruit and vegetables respectively, while plasma or serum concentrations of ascorbic acid, lutein and β-cryptoxanthin increased across the groups in a dose-dependent manner. For each 1 portion increase in reported fruit and vegetable consumption, there was a 6.2% improvement in forearm blood flow responses to intra-arterial administration of the endothelium-dependent vasodilator acetylcholine (p=0.03). There was no association between increased fruit and vegetable consumption and vasodilator responses to sodium nitroprusside, an endothelium-independent vasodilator.

**N02030 – A dose response study of the effects of increased fruit and vegetables intake on vascular function**

Professor Tom Sanders presented on the FSA funded dose response study examining the effects of increased fruit and vegetables intake on vascular function.

The aim of this study was to investigate whether increasing the intake of potassium rich fruit and vegetables from the UK average of 3 portions a day to the recommended level (~5 portions a day providing an additional 20 mmol K) or higher (approximately 10 portions a day providing 40 mmol K) lowers blood pressure among subjects with high normal blood pressure. The effects of an increased intake of potassium when provided as a 40 mmol potassium citrate supplement were also explored. The primary outcome measure was a change in ambulatory blood pressure and the secondary outcome measure was a change in arterial stiffness and endothelial function measured as carotid to femoral pulse wave velocity and flow mediated dilatation of the brachial artery respectively.

Forty eight subjects with diastolic blood pressure > 80 and < 100mmHg participated in the study. Prior to commencing the trial, participants underwent a 3 week run-in period on the control level of fruit and vegetable intake. This run-in period was to habituate the subjects to the dietary intervention and the ambulatory BP measurements and the vascular function measurements. A randomized placebo-
controlled crossover orthogonal design was then used to compare 3 experimental versus a control treatment. Each treatment period lasted 6 weeks and was separated from the next treatment by a minimum 5 weeks, where subjects were allowed to revert to their usual diet. The control treatment involved consuming placebo capsules (2 capsules taken 4 times a day) and an intake of fruit and vegetables similar to the average UK intake, the experimental treatments compared an additional 20 or 40 mmol potassium/d provided as fruit and vegetables or 40 mmol/d as potassium citrate capsules (2 capsules taken 4 times a day). Personalized dietary advice was provided as a unit system (1 unit = 5 mmol potassium) and the participants were provided with fruit and vegetables free of cost for the duration of the intervention. Participants were blinded to allocation of placebo and potassium citrate capsules, which were matched in size and colour. Measurements were carried out at the end of each treatment period and researchers undertaking vascular function measurements were blinded to all treatment allocations.

Compliance to the dietary intervention was good as measured by self reported fruit and vegetable intakes, capsule counts and 24 hour urinary potassium collection. Overall no changes in ambulatory blood pressure, arterial stiffness, endothelial function or serum CRP was observed.

Discussion

The workshop highlighted that the FSA is funding some of the largest and most well powered intervention trials investigating the type of fat and CHO, whole grains, and fruit and vegetable consumption on various cardiovascular health risk factors. These trials are of long duration with sufficient subject numbers and power to detect clinically important effects.

The majority of the studies presented did not demonstrate strong associations with the primary outcome measures. Further investigation into type of whole grain and type of fruit and vegetable may explain the differing effects observed between the two whole grain studies and two fruit and vegetable studies respectively.

The studies presented as part of the workshop acknowledged the value of a run in phase prior to the intervention trial as a way of decreasing the number of drop outs during the main intervention. The nature and length of the run in phase will depend on the type of intervention.

The present workshop also highlighted that one of the largest nutritional/dietary factors for CVD risk is body weight. It was identified that there is a need for future studies to focus more on weight control as an important modulator of CVD risk.

Results from all these trials will substantively add to the evidence base in their specific areas.

Recommendations

- Encouragement of all future intervention trials to be statistically well powered.
- All future trials should consider the inclusion of run in phase.
Research recommendation

- Investigations into foods with intact grain for example muesli, oats versus processed wholegrain foods like bread.
- Further investigation into the different types of fruit and vegetables and CVD risk.
- Further studies to focus on weight control and the risk of CVD.

Attendees

Professor Philip Calder, University of Southampton; Dr Susan Jebb, Dr Carmel Moore and Mark Chatfield, MRC Human Nutrition Research, Cambridge; Dr Bruce Griffin, University of Surrey; Dr Julie Lovegrove, University of Reading; Professor Gary Frost and Dr Louise Goff, Imperial College London; Dr Frank Thies and Dr Paula Tighe, University of Aberdeen; Professor Gary Duthie, Rowett Research Institute; Professor Chris Seal and Dr Iain Brownlee, Newcastle University; Professor Tom Sanders, Kings College London; Dr Jayne Woodside and Dr Damian McCall, Queens University Belfast; Dr Paul Haggarty, Rowett Research Institute (SACN); Dr John Stanley, Trinity College and St Hugh’s College, Oxford (N02 Programme Advisor); Dr Alison Tedstone, Dr Elaine Stone, Ms Emma Peacock, Ms Rachel Elsom, Ms Vicki Pyne and Ms Jill Pit, Food Standards Agency, London, UK.

References


