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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 carbohydrates 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.

UK Food Standards Agency workshops: Carbohydrates: Cardiovascular health

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 carbohydrate and fat, whole grains, and fruit and vegetables, on 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; whole grain; 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

CVD is the leading cause of death worldwide and the WHO suggests that one-third of all global deaths (15·3 million) are caused by CVD[1]. 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[2]. In the UK in 2006, CVD accounted for 197 767 deaths or 35 % of all deaths, of which 94 381 were from CHD and 55 098 deaths from stroke[2]. 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[2].

Abbreviations: FSA, Food Standards Agency; GI, glycaemic index.

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The burden of CVD is a major public health concern, and there is convincing evidence that dietary and nutritional factors can reduce risk[1]. 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 (for example, 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 CVD

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 dyslipideaemia, insulin resistance and hypertension, an earlier FSA workshop[3] 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 dyslipideaemia or hypertension.

Dietary fat, carbohydrate and CVD

Current dietary recommendations for the UK advise the consumption of no more than 10 % of dietary energy from saturated fat[4]; however, current intakes in the UK population average 13 %[5]. There is evidence to suggest that a diet high in saturated fat (SFA) increases the concentration of total cholesterol, particularly LDL-cholesterol, in the bloodstream, which is strongly associated with increased risk of CVD[6]. On the other hand, replacing fat with carbohydrate decreases HDL-cholesterol, which is also associated with increased risk of CVD[7]. However, cross-sectional studies have suggested that the HDL-lowering effect of carbohydrate may be influenced by the glycaemic index (GI) of the diet[8,9]. The Prospective Trialists' Collaboration[6] 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 & Mann[10] 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[11]. One hundred and sixty-two subjects were randomised to either a high-SFA or a high-monounsaturated fat (MUFA) diet. Insulin sensitivity measured by intravenous glucose tolerance test was significantly lowered by the high-SFA diet but not by the high-MUFA diet. A *post hoc* analysis suggested that this effect of MUFA only occurred in the subjects that consumed total fat below 37 % of energy.

In another randomised cross-over trial[12], fifty-nine subjects followed a SFA-rich diet for 28 d and were then randomised to a low-fat, high-carbohydrate diet or a high-MUFA diet ('Mediterranean diet') for 28 d in each group. Both diets demonstrated an improvement in insulin sensitivity compared with 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. Pérez-Jiménez *et al.*[13] reported that a high-MUFA diet decreased plasma von Willebrand Factor, tissue factor pathway inhibitor and plasminogen activator inhibitor-1 concentrations in twenty-five healthy male subjects. Similarly Fuentes *et al.*[14] observed an improvement in vascular function measured by flow-mediated dilatation in twenty-two hypercholesterolaemic men consuming a high-MUFA diet. Keogh *et al.*[15] also reported that a high-SFA diet resulted in significant deterioration in flow-mediated dilatation of the brachial artery compared with the high-PUFA, -MUFA or -carbohydrate diets. In comparison, Ashton *et al.*[16] observed no effect of a modified fat (with a high MUFA content) or a low-fat, high-carbohydrate diet on arterial elasticity in twenty-eight healthy subjects. No effect on flow-mediated dilatation of the brachial artery was observed in a randomised cross-over trial of thirty-two healthy subjects consuming a low-fat-diet[17].

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 on the metabolic syndrome.

N02031 – Impact of the amount and type of dietary fat and carbohydrate on the 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 carbohydrates on the metabolic syndrome.

The main aims of the RISCK (University of Reading, Imperial College, University of Surrey, MRC Human Nutrition Research, Cambridge and King's College London) study were 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 the 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:

(1) the reference diet – high-SFA, high-GI (38 % energy from fat, 18 % energy from SFA, 12 % energy from MUFA, 6 % energy from PUFA and 45 % energy from carbohydrates);
(2) high-MUFA, high-GI diet (38 % energy from fat, 10 % energy from SFA, 20 % energy from MUFA, 6 % from PUFA and 45 % from carbohydrates);
(3) high-MUFA, low-GI diet (38 % energy from fat, 10 % energy from SFA, 20 % energy from MUFA, 6 % from PUFA and 45 % from carbohydrates);
(4) low-fat, high-GI diet (28 % energy from fat, 10 % energy from SFA, 12 % energy from MUFA, 6 % energy from PUFA and 55 % energy from carbohydrates);
(5) 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 carbohydrates).

To achieve the fat and carbohydrate modification, sources of fat and carbohydrates were replaced with study foods specifically developed with relevant fatty acid profile and carbohydrate content[18].

Subjects completed a 4-week run-in phase where the reference diet was consumed before 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 drop-outs occurred during the run-in phase before the main intervention period.

The study was powered to measure the primary outcome measure insulin resistance, which was measured by reduced sampling intravenous glucose tolerance test 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[19].

The screening tool successfully identified participants predisposed to CVD. The 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 postprandial measures of insulin sensitivity was observed. The replacement of SFA with either MUFA or carbohydrates 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 carbohydrates and the effect on metabolic syndrome and CVD risk factors.

Whole-grain consumption and CVD

There is good epidemiological evidence demonstrating a protective effect of high consumption of whole grains against CVD risk[20–22]. A meta-analysis of twelve cohort studies[23] concluded that subjects with the highest intake of whole grain had about 26 % lower risk of developing CHD compared with those with the lowest intake. An update on this meta-analysis, which included thirteen studies, reported a 29 % reduction in CHD risk. In a recent meta-analysis of seven prospective cohort studies[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[25] analysed ten randomised controlled trials on wholegrain foods and effects on CHD mortality, morbidity and on risk factors for CVD. 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, eight out of the ten 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 wholegrain 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 d have a cardioprotective 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.

A total of 233 healthy subjects aged 40–65 years with a BMI of 25–35 kg/m^2 were randomised into one of three intervention groups: control (refined-cereal diet, avoidance of wholegrain foods); whole-wheat diet (three servings of wholegrain foods); or whole-wheat and -oat diet (three servings of wholegrain foods, including oats). Before 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 three portions of wheat or wheat and oat whole grains.

The primary outcome measures of this study were total and LDL-cholesterol concentrations (the study was powered on these two markers). Blood pressure, lipoprotein profile, inflammatory markers and arterial stiffness were also measured at each time point.

In total, 206 subjects completed the study. Macronutrient intake did not change throughout the trial, except for NSP, which increased in the whole-grain intervention groups. Systolic blood pressure and pulse pressure significantly decreased in the wholegrain food groups compared with 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 CVD 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 upon Tyne and Cambridge. A total of 266 subjects (aged 18–65 years; BMI $> 25\,kg/m^2$) who habitually consumed $< 1{\cdot}5$ portions of whole grain/d were recruited across the two centres. Subjects were randomised to one of three groups: control group (no dietary intervention); three servings of whole grain per d for 16 weeks; or three servings of whole grain per d for 8 weeks followed by six servings of whole grain per d for 8 weeks. Wholegrain foods (for example, 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 FFQ. Plasma was analysed for lipid profile (total, LDL- and HDL-cholesterol and TAG concentrations), insulin and glucose and 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 < 20 g/d 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 20 g/d throughout the study and during the 12-month follow-up period. For the three servings group, whole-grain intake was about 70 g/d for weeks 8 and 16, and for the second intervention group whole-grain intake was 76 g/d at week 8 and 115 g/d 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[26]. 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[27,28]. These data do not support the observational data for the health benefits of wholegrain foods, although the intervention may be too short to change the lifelong disease trajectory associated with CVD in 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 vegetables and CVD

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 nine cohort studies[29] reported a beneficial association between fruit and vegetable consumption and CHD risk. A more recent meta-analysis of thirteen cohort studies[30] demonstrated a 17 % decrease in CHD risk from increasing fruit and vegetable consumption from less than three portions to more than five portions per d. A small, slightly significant decrease in CHD risk was also noted where intake was increased to between three and five portions per d. A pooled analysis of nine cohort studies showed that increased fruit and vegetable intake was associated with a reduced risk of stroke[31]. Individuals who consumed more than five servings per d had a significantly reduced risk of stoke compared with individuals who had less than three servings per d. 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 mmHg on the fruit and vegetable diet and 4·6/2·6 mmHg on the combination diet compared with changes of $-0{\cdot}2/+0{\cdot}1$ mmHg on the control diet[34]. The blood pressure-lowering effects of the diets were greater in those with raised blood pressure.

A 6-month randomised controlled trial used a brief negotiation method to encourage increased consumption of fruit and vegetables to at least five portions per d[35]. Subjects reported an increase in average fruit and vegetable consumption from 3·4 to 4·9 portions per d, which resulted in a decrease in systolic blood pressure by 4·0 mmHg and diastolic blood pressure by 1·5 mmHg 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. A total of 147 volunteers were recruited, with 117 of them completing the 4-week run-in phase where all

subjects were limited to one portion of fruit and vegetables per d. Following the run-in phase, subjects were randomised to one of three intervention groups, where they consumed either one, three or six portions per d for 8 weeks. Compliance to the dietary intervention was measured by contemporaneous 4 d 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 one, three and six portions per d 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 one-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[37].

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

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

The aim of this study was to investigate whether increasing the intake of K-rich fruit and vegetables from the UK average of three portions per d to the recommended level (about five portions per d, providing an additional 20 mmol K) or higher (approximately ten portions per d, providing 40 mmol K) lowers blood pressure among subjects with high normal blood pressure. The effects of an increased intake of K 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.

A total of forty-eight subjects with diastolic blood pressure >80 and <100 mmHg participated in the study. Before 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 blood pressure and vascular function measurements. A randomised placebo-controlled cross-over orthogonal design was then used to compare three experimental *v.* a control treatment. Each treatment period lasted 6 weeks and was separated from the next treatment by a minimum of 5 weeks, where subjects were allowed to revert to their usual diet. The control treatment involved consuming placebo capsules (two capsules taken four times per d) and an intake of fruit and vegetables similar to the average UK intake; the experimental treatments compared an additional 20 or 40 mmol K/d provided as fruit and vegetables or 40 mmol/d as potassium citrate capsules (two capsules taken four times per d). Personalised dietary advice was provided as a unit system (1 unit = 5 mmol K) 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 h urinary K collection. Overall no changes in ambulatory blood pressure, arterial stiffness, endothelial function or serum C-reactive protein concentration were 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 carbohydrates, whole grains, and fruit and vegetable consumption on various CVD 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 vegetables 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 before 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 nutrition- and diet-related 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

(1) Encouragement for future intervention trials to be statistically well powered.
(2) Future trials should consider the inclusion of a run-in phase.

Research recommendations

(1) Investigations into foods with intact grains, for example, muesli or oats *v.* processed wholegrain foods such as bread.
(2) Further investigation into the different types of fruit and vegetables and CVD risk.
(3) 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, King's College London; Dr Jayne Woodside and Dr Damian McCall, Queen's University Belfast; Dr Paul Haggarty, Rowett Research Institute (Scientific Advisory Committee on Nutrition; 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 Pitt, FSA, London, UK.

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