The relation between diet/nutritional factors and the risk of pre-diabetes and type 2 diabetes, and implications for prevention

Scope of the expert testimony: This paper covers the context of diet/nutrition in promoting diabetes risk, the evidence for association of potentially important candidate dietary factors with diabetes risk, and areas for future directions and policy implications for the prevention of diabetes/pre-diabetes. *What this paper will not cover:* It will not provide an exhaustive review of all potential dietary factors for which there is some existing or emerging evidence. It will also not describe the mechanism of association with diabetes/pre-diabetes for candidate nutritional factors, which are most often comprehensively discussed within the scientific papers referenced here. The average intakes in the UK of many of the foods/nutrients appraised herein are provided by the National Diet and Nutrition Surveys (http://www.food.gov.uk/science/dietarysurveys/).

Context: The importance of diet and challenges of nutritional epidemiology
Primary prevention trials have demonstrated that lifestyle intervention with a healthy diet and physical activity are at least as effective as pharmacological interventions in reducing typ2 diabetes incidence among those at high risk.[1] Such lifestyle interventions continue to have benefit long after the active phase of the intervention.[2;3] Diet/nutrition offers a potentially modifiable risk factor for the prevention of pre-diabetes and diabetes in the general population too.[4] However, despite the potential importance of diet/nutrition in the causation of diabetes, there remains continuing uncertainty about the exact nature of such associations. Not helped by the challenges of measuring diet/nutrition and dietary behaviours, the differences in methods and exposure definitions used in different studies, and the potential for inadequate control of confounding, there are many conflicting findings, the association between fish intake and the risk of diabetes being a case in point.[5;6] Intervention trials of diet/nutrition components for chronic disease end-points are particularly challenging, and trials of dietary supplements, primarily for vitamins/anti-oxidants, are more amenable to design and conduct. However, this has often led to further confusion, with a disconnect between observational epidemiology and trial evidence.[7;8] We have to accept that the conventional hierarchy of evidence cannot always be applied to nutritional factors, and policy decisions have to be based on best available evidence that is feasible and pragmatic in the public health context.

Some key candidate diet/nutrition factors for the prevention of type 2 diabetes/pre-diabetes
Points to note: the effects described are from the highest level of evidence available; and present comprehensively adjusted data, including for obesity (mostly BMI, often waist circumference additionally), dietary factors and social-demographic factors.

Fruit and vegetable intake
A previous systematic review did not find significant association between fruit/vegetable intake and diabetes risk.[9] An updated systematic review (under review at BMJ), has reported that greater (highest versus lowest) intake of green leafy vegetables resulted in a 14% (hazard ratio 0.86, 95%CI 0.77-0.97) reduction in risk of type 2 diabetes, while there was no significant association with total intake of vegetables, fruit or fruit and vegetables combined.[10] We have reported a striking dose response inverse association between

plasma vitamin C and risk of incident diabetes but a more modest association with self-reported fruit/vegetables in a head to head methodological comparison in the EPIC Norfolk cohort.[11] We were careful to account for potential confounders especially clustering of behaviours that might accompany plasma vitamin C levels. Our results need to be confirmed in other populations but point to the enhanced utility of objectively measured biomarkers of nutritional exposures when these can be identified. It is likely that the current recommendations for increased fruit/vegetable intake for other chronic diseases will also benefit pre-diabetes/diabetes risk, but the Leicester group's systematic review suggests that tailored advice of specific items might be warranted for diabetes prevention. Further research is needed in this area**.**

Meat intake

Two meta-analyses show consistent findings for processed meat intake. In a meta-analysis of 12 cohort studies, Aune et al reported significant increased risk of diabetes comparing 120 g/d higher serving of red meat [RR 1.20 (95%CI 1.04-1.38)], and 50 g/d higher serving of processed meat [RR 1.57 (1.28-1.93)].[12] Micha's meta-analysis published June 2010 included nearly 11,000 diabetes cases (and also investigated associations with coronary heart disease (CHD) and stroke).[13] Non-processed red meat (per 100 g/d) showed a non-significant trend towards association with diabetes [RR 1.16 (0.92-1.46)], but a 50 g/d serving of processed meat was significantly associated with a 19% increased risk of diabetes [RR 1.19 (1.11-1.27)], and risk for total meat (red or processed) was intermediate. It is not clear if the different findings for red meat are due to methodological differences between the two reviews, including a different portion size included for red meat, while the same portion size (50 g/d) for processed meats was used in each review. Nonetheless, there is consistent finding from two large systematic reviews for a positive association between processed meat intake and type 2 diabetes. Both reviews acknowledge their potential limitations, inherent in the individual included studies. Studies were observational (no randomized trials were identified), but attempts were made to take into account confounding factors. The consistency of association for processed meat intake and diabetes risk cannot be ignored.

SACN is currently appraising the evidence for the benefits and harms of meat intake within the context of iron status and health.[14] The World Cancer Research Fund (WCRF) 2007 report recommended dietary advice to reduce red meat intake (including processed meats) following its scientific appraisal showing "convincing evidence for association with colorectal cancer risk".[15] However this has been hotly debated, and the SACN report is eagerly awaited. The current average intake of red meat is approximately 70 g/day in the UK, but 33% of UK adults are considered high consumers (100 g/d or more)[14]

Fish intake

There is currently conflicting evidence for the intake of fish in relation to prevention of diabetes.[5;6;16] Further research is needed, and current dietary advice on fish intake should continue be followed.[17] In light of the limitations of self-report dietary assessment methods combined with the availability of valid biomarkers of fish intake (omega-3 fatty acids of marine origin in blood fractions) it is a vital next step**.** This is being addressed within the FP-6 EU-funded InterAct project (www.inter-act.eu).

Sugar sweetened beverages

Sugar sweetened beverages (SSBs) are implicated in fuelling the obesity epidemic, but there is accumulating evidence that they are also, independently of obesity, associated with risk of insulin resistance and diabetes, as well as cardiovascular disease.[18] The American Heart Association recently issued a statement recommending reductions in added sugar intake to no more than 100 to 150 kcal/d for most Americans, identifying SSBs as the primary source of added sugars in the American diet.[19] Preliminary findings from a meta-analysis (8 studies) reported a significant 28% (95%CI 14-53%) elevated risk of type 2 diabetes incidence in those consuming highest versus lowest SSBs in adjusted analyses that included studies with adjustment for energy intake and BMI but the risk was 33% (12-46%) higher when excluding such studies (unpublished findings: presented at a scientific talk; Malik V, Hu FB et al 2010). UK trends show increasing soft drink consumption and their contribution to non-milk extrinsic sugars.[20] With the convincing evidence for SSBs effects on obesity, and also accumulating evidence for diabetes, further research is needed in the UK (for diabetes endpoint), accompanied by urgent action in parallel to formulate specific policy on their intake in the UK.

Carbohydrate intake, glycaemic index, fibre and whole-grain foods

Both the amount and type of carbohydrate consumed have an effect on insulin secretion and postprandial glycaemia. The concept of glycaemic index (GI) quantifies the glycaemic response to carbohydrates in different foods and provides a biologically meaningful ranking of carbohydrate-containing foods. Glycaemic load (GL) is the mathematical product of the GI of a food and its carbohydrate content, indicating the glucose response and insulin demand of a food serving. Previously inconsistent findings have led the way for meta-analysis showing a positive independent association between both GI and GL and incident diabetes, with lower GI being associated with lower diabetes risk.[21] Note that SSBs have high GL. There is increasing meta-analytical evidence that cereal fibre[22] and whole grain foods[23;24] are inversely associated with reduced diabetes risk. Mean non-starch polysaccharide (NSP) fibre intake remains low in the UK,[20] and action is needed to enhance its intake for diabetes prevention.

Fat intake

In June 2010, NICE released recommendations and plan of action to reduce dietary saturated fat intake and eliminate industrially produced trans fats for the prevention of cardiovascular disease.[25] The evidence for association of fat intake with diabetes has been mixed, but largely consistent with the view that improving fat quality by replacing saturated fats (SFA) with polyunsaturated fats (PUFA) or mono-unsaturated fats (MUFA) is beneficial both for improved insulin sensitivity (in trials of surrogate endpoints) and diabetes incidence (epidemiological studies).[26]. However, Micha and Mozaffarian critically examined the evidence for saturated fat intake and diabetes risk and found a null effect.[27] Rarely available, evidence from a large trial of SFA intake reduction (largely substituted by carbohydrates) found no reduction in markers of insulin resistance or diabetes incidence.[28]

While reduction of saturated fats is important, it is vital to consider the replacement nutrients consumed in place of the saturated fats. In USA secular trends show that reductions in energy intake and saturated fats have occurred, but with concomitant

increases in carbohydrates rather than MUFA or PUFA.[29] UK data show a similar pattern over 10 years, with reduced intake of energy from total fat, saturated fat, trans fats and cis-MUFA fats, and an increased intakes of % energy from carbohydrates.[20;30] Evidence is emerging that replacement of SFA with refined, high GI-value carbohydrates can significantly increase CHD risk. [27;31;32] Most carbohydrates in Western diets are highly processed and it is important to advocate that reduced SFA intake, when replaced with carbohydrates (as they often are), should include high fibre, less processed, lower glycaemic index (GI) carbohydrates. The conventional advice of low-fat, high carbohydrate diets for diabetes prevention are now challenged.[33] The inter-relationships between types of fat and carbohydrate are complex, but in the presence of obesity, refined carbohydrate intakes increase metabolic risk. Careful consideration needs to be given to the refined carbohydrate intake in the population for diabetes prevention.

Dietary patterns including Mediterranean diet

Development of dietary pattern analysis has offered a new direction in nutritional epidemiology, enabling examining whole diets rather than individual foods/nutrients. There is a growing evidence base, but not yet conclusive, that Mediterranean type diets reduce the risk of new diabetes.[34] Further evidence on this for obesity/pre-diabetes will be considered in a separate expert testimony.

Other dietary factors

Diet consists of tens of thousands of individual food items and nutrients including macro- and micro- nutrients. While there is growing evidence for association with diabetes for many of these, the causal association and mechanisms of action are often unclear.

Implications for prevention

(1) The balance of a high risk approach versus a whole population approach has been debated for diabetes prevention. The diabetes primary prevention trials were all based among high risk groups,[1] but the effectiveness of the trials' lifestyle behaviours has been demonstrated in the general population.[35] It is likely that in the vast majority of situations whole population dietary interventions will work best. (2) With primary research focus on diet/diabetes associations, very little evidence exists for understanding the determinants and antecedents of dietary behaviour and food choice. These determinants may work at the individual level, depending on personal biological, social, cultural, religious, psychological or economic factors. There is increasing awareness, however, that there are wider determinants of risk behaviours, operating at the population level. We need to gain a greater understanding of individual and collective level determinants to enable behaviour change for the prevention of pre-diabetes and diabetes. For instance, the action to call for a ban on industrially produced trans fats and legislation on amount permitted in fats/oils in food manufacturing and cooking will reduce its consumption.[25] Similar type of action is warranted for diabetes prevention, targeting key nutritional exposures.

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