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Review article

Diet composition and the risk of type 2 diabetes: epidemiological and clinical evidence

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In the last 10 years nutritional research on diabetes has improved dramatically in terms of both number of studies produced and quality of methodologies employed. Therefore, it is now possible to attempt to provide the evidence on which nutritional recommendations for the prevention of type 2 diabetes could be based. We therefore performed a literature search and, among the papers published in indexed journals, we selected relevant epidemiological (mostly prospective) and controlled intervention studies. Lifestyle factors that have, so far, been consistently associated with increased risk of type 2 diabetes are overweight and physical inactivity. However, recent evidence from epidemiological studies has shown that the risk of type 2 diabetes is also associated with diet composition, particularly with: (1) low fibre intake; (2) a high *trans* fatty acid intake and a low unsaturated:saturated fat intake ratio; (3) absence of or excess alcohol consumption. All these factors are extremely common in Western populations and therefore the potential impact of any intervention on them is large: indeed, >90 % of the general population has one or more of these risk factors. The ability to correct these behaviours in the population is estimated to reduce the incidence of diabetes by as much as 87 %. Recent intervention studies have shown that type 2 diabetes can be prevented by lifestyle changes aimed at body-weight reduction, increased physical activity and multiple changes in the composition of the diet. Within this context, the average amount of weight loss needed is not large, about 5 % initial weight, which is much less than the weight loss traditionally considered to be clinically significant for prevention of type 2 diabetes. In conclusion, new emphasis on prevention by multiple lifestyle modifications, including moderate changes in the composition of the habitual diet, might limit the dramatic increase in incidence of type 2 diabetes envisaged worldwide.

Type 2 diabetes: Prevention: Lifestyle: Carbohydrate: Fat: Fibre

Diabetes mellitus is a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia and associated with impaired carbohydrate, fat and protein metabolism. These abnormalities are the consequences of either inadequate insulin secretion or impaired insulin action, or both. Diabetes has been recently reclassified into four distinct types: type 1; type 2; gestational diabetes mellitus; other specific types (American Diabetes Association, 1997; World Health Organization, 1999).

Type 2 diabetes mellitus, until recently referred to as non-insulin-dependent diabetes, accounts for about 85–95 % of all disease cases. In Western countries the estimated prevalence in the population is 4–6 %: half of these cases are diagnosed, while a similar number remains unrecognised. The disease is observed much more frequently in older people and in some ethnic communities (up to 40 % of Pima Indians). WHO has predicted that the global prevalence of type 2 diabetes will more than double from 1995 to 2025, from 135 million to 300 million (King *et al.* 1998; Choi & Shi, 2001).

Long-term complications of type 2 diabetes include retinopathy (with potential loss of vision) nephropathy (leading to renal failure), peripheral neuropathy (with risk of foot ulcers and gangrene), and autonomic neuropathy (which contributes to erectile dysfunction and cardiac arrhythmia). However, most of the morbidity and mortality associated with diabetes is attributable to macrovascular complications, such as myocardial infarction and acute stroke. Diabetes is associated with an age-adjusted cardiovascular mortality between 2- and 4-times that of the non-diabetic population, while life expectancy is reduced by 5–10 years in middle-aged patients with type 2 diabetes (Stamler *et al.* 1993; Uusitupa *et al.* 1993; United Kingdom Prospective Diabetes Study, 1998; Roselli della Rovere *et al.* 2003).

Patients with type 2 diabetes are treated with diet, oral agents or insulin in order to keep their blood glucose

Abbreviations: GI, glycaemic index; GL, glycaemic load.

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levels as close as possible to normal; treatment is aimed at relieving symptoms and at reducing the risk of long-term complications, which increase linearly with the degree of derangement of the metabolic control. However, although the treatment of diabetes has become highly sophisticated, optimal blood glucose control is not reached in most cases; moreover, microvascular and macrovascular diseases are already present in many individuals with undiagnosed or newly diagnosed type 2 diabetes. Therefore, prevention of diabetes has been authoritatively proposed as a promising approach to drastically reduce the huge burden resulting from the complications of diabetes (American Diabetes Association and National Institute of Diabetes, Digestive and Kidney Diseases, 2002).

The importance of lifestyle modifications for the prevention of type 2 diabetes has long been recognised. Several observational studies suggest that diabetes is primarily a lifestyle disorder; the highest prevalence rates occur in developing countries and in populations undergoing 'westernisation' or modernisation. Under such circumstances, genetic susceptibility seems to interact with environmental changes, such as sedentary life and overnutrition, leading to type 2 diabetes. Populations such as Nauru or Pima Indians, who have the highest reported prevalence of diabetes, share the common experience of environmental changes since they abandoned their traditional hunter–gatherer or agricultural-based lifestyle for sedentary living and a diet of energy-dense processed foods (West, 1978; O'Dea, 1992).

However, until very recently, the evidence available to support lifestyle modifications to prevent type 2 diabetes has been weak and often inconsistent, and therefore any advice to high-risk individuals or to the general population has so far been largely based on personal views or, at the very best, on a consensus of experts. In the last 10 years nutritional research on diabetes has improved dramatically in terms of both number of studies produced and quality of methodologies employed. Therefore, it is now possible to attempt to provide the evidence on which nutritional recommendations for the prevention of type 2 diabetes could be based.

Weight and low physical-activity levels represent the most important risk factors for type 2 diabetes; therefore, any strategy for diabetes prevention should consider lifestyle modification aimed at weight reduction and regular physical exercise (American Diabetes Association and National Institute of Diabetes, Digestive and Kidney Diseases, 2002). However, in this regard, sustained behavioural changes are hard to achieve; in addition, the general trend in the last few years has been towards an increased prevalence of overweight and a progressive decline in physical activity levels, especially among children and adolescents (Deckelbaum & Williams, 2001). Conversely, evidence is accumulating that diet composition, besides energy intake, also influences the risk of type 2 diabetes; therefore, it may be wise to attempt a multifactorial approach to diabetes prevention by introducing multiple small changes to adjust unhealthy lifestyles. This approach might facilitate compliance and maximise the metabolic effects.

Against this background, we reviewed the literature on diet and type 2 diabetes risk to take advantage of all the relevant information available, trying not only to collect data, but also, whenever possible, to compare studies based on different methodologies and thus provide the reader with all the information necessary to evaluate the consistency and strength of the associations between each specific dietary factor and the prevention of type 2 diabetes. Moreover, whenever possible, we have also tried to gather information on the possible effects of diet on the pathophysiological mechanisms of type 2 diabetes, as this would facilitate the evaluation of a cause–effect relationship between a specific diet component and type 2 diabetes.

Methods

We performed a literature search (MEDLINE) in September 2003 on dietary factors (fat, protein, carbohydrate, glycaemic index (GI) and glycaemic load (GL), sugars, fibre, alcohol, dietary patterns) and type 2 diabetes risk. The search produced 310 original papers, from which we selected all the epidemiological (mostly prospective) and controlled intervention studies relevant to the topic of this review (*n* 63).

Relationship between diet, insulin sensitivity and the development of type 2 diabetes

Energy

Overweight is by far the most important risk factor for type 2 diabetes. Almost 70–80 % of type 2 diabetic patients are either overweight or obese; moreover, several long-term prospective studies have shown a higher risk of diabetes with increasing body weight (Bennet *et al.* 1971; Knowler *et al.* 1981; Larsson *et al.* 1981; Van Itallie, 1985; Ohlson *et al.* 1988; Lundegren *et al.* 1989; Curb & Marcus, 1991; Perry *et al.* 1995; Maggio & Xavier, 1997).

In most studies the relationship between body weight and the risk of diabetes is continuous and graded (Colditz *et al.* 1990). The degree of overweight and the distribution of fat are important in the development of diabetes. An upper body or central distribution of body fat, independently of the absolute level of obesity, increases the risk of diabetes (Lapidus *et al.* 1984; Ohlson *et al.* 1985; Björntorp, 1992; Chan *et al.* 1994; Boyko *et al.* 2000; Samaras & Campbell, 2000). Abdominal fat can be evaluated by anthropometric measurements, such as waist circumference, waist:hip cirumference ratio, sagittal abdominal diameter or by instrumental techniques such as computerised tomography or nuclear magnetic resonance imaging (specifically to measure visceral fat). Patients with central adiposity (waist circumference $>1{\cdot}02$ m in male and $>0{\cdot}88$ m in female patients) have higher insulin levels and are more insulin resistant than subjects with a similar weight but a peripheral-type of obesity (Abate *et al.* 1997; Samaras & Campbell, 2000; Laaksonen *et al.* 2003). Abdominal adipose tissue not only has a greater metabolic activity but also is anatomically positioned closer to the liver, implying a greater flux of NEFA going to the liver. This, in turn, can interfere with glucose oxidation and hepatic extraction of insulin. There is evidence indicating that elevated plasma NEFA levels

could also impair insulin secretion at the level of the pancreatic β-cells (Boden, 1996; Wiesenthal *et al.* 1999; Frayn, 2000).

Observational data from the Framingham Study on 618 overweight subjects showed the effects of weight loss on risk of diabetes. Sustained weight loss led to a 37 % lower risk of diabetes (relative risk 0·63 (95 % CI 0·34, 1·20)) and this effect was stronger for more obese people (BMI > 29; relative risk 0·38 (95 % CI, 0·18, 0·81)). In particular, those who lost 3·7–4·5 kg had a 33 % reduction in diabetes risk, whereas those losing more weight had a 51 % reduction in risk (Moore *et al.* 2000).

The importance of overweight in relation to the risk of type 2 diabetes has been confirmed by intervention studies showing that a reduction of body weight decreases the incidence of diabetes (Toumìlehto *et al.* 2001; Diabetes Prevention Program Research Group, 2002). In addition, in those already affected by the disease, weight loss reduces fasting hyperglycaemia as a consequence of the reduced postabsorptive rates of hepatic glucose production. Furthermore, weight loss improves insulin sensitivity in peripheral tissues and, in particular, increases the capacity of non-oxidative glucose metabolism (Henry *et al.* 1986*a*,*b*; Albu *et al.* 1997).

Diet composition can influence the development of type 2 diabetes by affecting body weight. However, the evidence available in the literature is incomplete and in particular lacks information from properly designed randomised intervention trials. Laboratory experiments in animals and clinical studies in human subjects have repeatedly shown that dietary factors, particularly fat and energy intakes, are strongly and positively associated with excess body weight. By contrast, the population-based studies on diet and obesity have yielded inconsistent results due to a number of factors, including weakness in the study design and systematic measurement errors in dietary data (Riccardi *et al.* 2004).

Excessive body-fat deposition is a consequence of an imbalance between energy intake and energy expenditure; therefore, since the majority of the population have sedentary lifestyles, it is energy intake that really matters in relation to the development of overweight, and energy intake is often high when fat-rich foods are consumed in large amounts (Astrup, 2001); nevertheless, in some cases, particularly in children and adolescents, excessive consumption of carbohydrate-rich foods (soft drinks) may be predictive of overweight (Ludwig *et al.* 2001). There is also evidence that consumption of a low-energy (high fibre) diet reduces energy intake, thus facilitating weight reduction (Yao & Roberts, 2001). However, there are no long-term clinical trials examining the effects of diet composition on body-weight regulation.

Carbohydrates and fibre

Carbohydrate is traditionally classified as sugars, oligosaccharides and polysaccharides on the basis of its chemical structure (Bantle, 1989; Asp, 1994; Food and Agriculture Organization/World Health Organization, 1998). However, a classification based purely on their chemistry does not provide a ready guide to their importance for health. More important is classification based on their ability to be digested and absorbed in the human small intestine, thus contributing directly or indirectly to the body's carbohydrate pool (glycaemic carbohydrates); in this classification carbohydrates that are not digested and absorbed in the human small intestine are kept separate from glycaemic carbohydrates, and among them dietary fibre represents the most important group (Trowell, 1976; Cummings & Englyst, 1987, 1991; Parillo & Riccardi, 1995; Vinik & Jenkins, 1998). Carbohydrate-rich foods can also be classified on the basis of their effects on postprandial glycaemia, which can be expressed as GI. This index is based on the increase in blood glucose concentration (the incremental area under the curve of blood glucose concentration) after the ingestion of a portion of a test food containing 50 g carbohydrate, divided by the incremental blood glucose area achieved with the same amount (50 g) of carbohydrate present in an equivalent portion of reference food (glucose or white bread). Fibre-rich foods often have a low GI, although some foods with a low-fibre content may also have a low GI (Jenkins *et al.* 1982, 1984; Parillo *et al.* 1985; Hollenbeck *et al.* 1986; Riccardi & Rivellese, 1987; Bjorck *et al.* 2000).

Several beneficial effects of high-fibre low-GI diets have been shown, including lower postprandial glucose and insulin responses, improved lipid control and, possibly, improved insulin sensitivity (Parillo *et al.* 1988; Fugawa *et al.* 1990; Riccardi & Rivellese, 1991; Frost *et al.* 1998; Wolk *et al.* 1999; Chandalia *et al.* 2000; Wolever, 2000; Ford & Liu, 2001). There is no exact value of a high- or low-GI diet. However, it seems clear that: (1) the lower the GI the better the metabolic effects; (2) the differences between a low- (< 70) and a high- (> 80) GI diet should be at least 10 % in order to achieve measurable metabolic effects (Willett *et al.* 2002).

In epidemiological studies the intake of either total carbohydrate or sugars (sucrose) does not predict the risk of diabetes (Yang *et al.* 2003). In particular, in most studies in which the relationship between intake of refined sugars and incidence of type 2 diabetes has been examined, the results show no positive association between sucrose consumption and risk of diabetes (Howard & Wylie-Rosett, 2002; Willett *et al.* 2002; Janket *et al.* 2003). Conversely, there is strong evidence that a diet rich in carbohydrate and fibre and with low GI may contribute to the prevention of diabetes prevention (Table 1). Some prospective studies have shown an inverse relationship between the consumption of fibre-rich foods and the risk of type 2 diabetes. In two of them a slight decrease in diabetes risk was also found with a low-GI diet compared with a high-GI diet (Salmeròn, 1997*a*,*b*). These results, however, have not been confirmed in all studies (Feskens & Kromhout, 1989; Lundgren *et al.* 1989; Feskens *et al.* 1995; Williams *et al.* 1999; van Dam *et al.* 2000; Hu & van Dam, 2001; Meyer *et al.* 2001; Stevens *et al.* 2002; Willett *et al.* 2002; Mantonen *et al.* 2003).

Since postprandial blood glucose response is influenced not only by the GI value of the food, but also by the amount of ingested carbohydrate, the concept of GL (the GI of a specific food multiplied by the amount of carbohydrate contained in an average portion of the food

Table 1. Major prospective studies on dietary carbohydrate, fibre and risk of type 2 diabetes

Study	Subjects (*n*)	Follow-up (years)	Diet assessment	Associations
Gothenburg (Lundgreen *et al.* 1989)	1462	12	24 h recall	No associations
Zutphen Study (Feskens & Kromhout, 1989)	841	25	Dietary history	No associations
Seven Countries Study (Feskens *et al.* 1995)	338	20	Dietary history	Inverse association with vegetables and legumes
Nurses' Health Study (140) (Salmeròn *et al.* 1997*b*)	65 173	6	FFQ	Inverse association with fibre; positive association with glycaemic load
Health Professionals' Study (Salmeròn *et al.* 1997*a*)	42 759	6	FFQ	Inverse association with fibre; positive association with glycaemic load
Iowa Women's Health Study (Meyer *et al.* 2001)	35 988	6	FFQ	Inverse association with fibre; no association with glycaemic index or glycaemic load
US adults (Ford & Mokdad, 2001)	9665	18	24 h recall	Inverse association with vegetable intake
ARIC Study (Stevens *et al.* 2002)	12 251	9	FFQ	Inverse association with cereal fibre
Finnish Mobile Clinic (Montonen *et al.* 2003)	4316	10	Dietary history	Inverse association with cereal fibre

ARIC, Atherosclerosis Risk in Communities; NHEFS, ; FFQ, food-frequency questionnaire.

consumed) has been developed in epidemiological studies to represent better the quantity and quality of carbohydrates consumed. Each unit of dietary GL represents the equivalent glycaemic effect of 1 g carbohydrate from white bread, which is used as the reference food (Willett *et al.* 2002). The Nurses' Health Study on 65 173 female subjects followed for 6 years, in which 915 new cases of diabetes developed, reports an increase in the incidence of diabetes in those consuming a diet with a higher GL, especially if in combination with a low intake of cereal fibre. In this study the relative risk of type 2 diabetes was 2·50 (95 % CI 1·14, 5·51) for women with the combination of high GL and low-fibre intake (GL$>$165 and cereal fibre $<$2·5 g/d *v.* GL$<$143 and cereal fibre $>$5·8 g/d) (Salmeròn *et al.* 1997; Liu *et al.* 2000). In addition, the GI of the diet was also positively associated with the risk of diabetes, with a continuous relationship from a low ($<$70) to medium (70–80) to high ($>$80) -GI diet ($P<0{\cdot}04$). These results have been confirmed in men in the Health Professionals' follow-up study (Salmeròn *et al.* 1997; Fung *et al.* 2002), but not in a recent analysis of the Iowa Women's Health Study, where a cohort of 35 988 older women from Iowa (USA) were followed for 6 years (1141 incident cases of diabetes were reported; Meyer *et al.* 2000). Despite the lack of association between GL and risk of diabetes, dietary fibre intake was also associated with a lower risk of diabetes. Indeed, the relative risk of diabetes in women in the highest quintile of consumption of wholegrain products (median value 20·5 servings per week) *v.* the lowest quintile (median value 1·0 serving per week) was 0·79 (95 % CI 0·65, 0·96; *P* for trend=0·009). Noteworthy is that in most prospective studies cereal fibre intake, in particular, is inversely associated with diabetes incidence (McKeown *et al.* 2002; Stevens *et al.* 2002; Montonen *et al.* 2003); however, fruit and vegetable consumption is also associated with a reduced risk of type 2 diabetes (Williams *et al.* 1999; Ford & Mokdad, 2001; Sargeant *et al.* 2001). Most of the epidemiological studies prospectively evaluating the relationship between dietary fibre intake and risk of type 2 diabetes are consistent in showing a protective effect of fibre consumption towards the development of diabetes.

There have not been any intervention studies evaluating the effect of fibre and/or GI on prevention of diabetes, although the most important intervention studies aiming at lifestyle modification also included an increase in fibre consumption in the intervention group (Tuomìlehto *et al.* 2001; Diabetes Prevention Program Research Group, 2002). In support of the role of fibre in the prevention of type 2 diabetes is evidence that reduced postprandial blood glucose levels contribute to reducing the risk of diabetes. Indeed all pharmacological and non-pharmacological interventions able to reduce postprandial glycaemia, with whatever mechanism, tested so far in people with pre-diabetes, have proven effective in the prevention of type 2 diabetes (Tuomìlehto *et al.* 2001; Chiasson *et al.* 2002; Diabetes Prevention Program Research Group, 2002; Hanefeld, 2002; Hanefeld & Temelkova-Kurkschiev, 2002).

Amount and type of dietary fat

Dietary fatty acids are classified as saturated, monounsaturated and polyunsaturated (*n*-6 and *n*-3 fatty acids) on the basis of their chemical structure (Feskens & van Dam, 1999; Marshall & Bessensen, 2002).

Early epidemiological studies reported that total fat intake was positively associated with the risk of diabetes (West & Kalbfleish, 1971). This effect was partly mediated by the influence of fat intake on weight gain, since fat-rich foods are generally energy-dense (irrespective of the type of fat). The type of fat predominantly used in these studies was also associated with the risk of diabetes (greater with animal fat than with vegetable fat). This has been subsequently confirmed by Kawate *et al.* (1979), who compared Japanese people living in Hawaii with those living in Japan and found that the former consumed twice as much animal fat and had a significantly higher prevalence of diabetes than the latter. Other studies, however, did not observe important associations between total fat intake and

incidence of type 2 diabetes, particularly when the influence of body weight was accounted for by appropriate statistical methodologies (Lundgren *et al.* 1989; Feskens *et al.* 1995). Table 2 shows the results of more recent prospective studies taking into account the total fat intake and the type of fat consumed. In the San Luis Valley Diabetes Study, 134 subjects with impaired glucose tolerance were followed for 3 years: fat consumption in those who developed diabetes was 43·4 % total energy intake compared with 40·6 % in those who still had impaired glucose tolerance (*n* 43) and 38·9 % in those who reverted to normal glucose tolerance (*n* 60). An increase in fat intake (40 g/d) was associated with a 6 % greater risk of developing diabetes (95 % CI 1·2, 29·8) (Marshall *et al.* 1991, 1994, 1997); saturated fat was also marginally associated with an increased risk of diabetes ($P=0·06$). In the Finnish and the Dutch cohorts of the Seven Countries Study total fat consumption and saturated fat intake contributed to the risk of type 2 diabetes (Feskens *et al.* 1995). In the Nurses' Health Study 84 204 women were followed prospectively for 14 years (Salmeròn *et al.* 2001). The main findings of this study, in which there were 2507 incident cases of type 2 diabetes, were: (1) no association between total fat, monounsaturated fat or saturated fat intake and incidence of diabetes; (2) a positive association between a higher *trans* fatty acid intake and risk of diabetes; (3) a negative association between a 5 % higher energy intake from polyunsaturated fat and incidence of diabetes (−35 %); (4) a positive association between intake of animal fat and incidence of diabetes (this relationship was no longer statistically significant after correcting for vegetable fat consumption). These data were subsequently confirmed by Meyer's study on 35 988 elderly women in Iowa (USA; Meyer *et al.* 2001). After an 11-year follow-up the authors reported 1890 incident cases of diabetes and found that vegetable fat intake was inversely related with incidence of diabetes; when comparing the highest category of vegetable fat intake with the lowest, the relative risk was 0·78 (95 % CI 0·67, 0·91). This result is mirrored by the finding of a positive association between animal fat consumption and diabetes incidence.

In the Health Professionals' Study, which included 42 504 male subjects followed for 12 years, total and saturated fat intakes were associated with a higher risk of type 2 diabetes (relative risk 1·27 and 1·34 respectively), but these associations disappeared after adjustments for BMI. However, there was an increased risk for diabetes in men who consumed processed meat at least five times per week compared with those who consumed processed meats less than once per month (relative risk 1·46; 95 % CI 1·14, 1·86) (van Dam *et al.* 2002*b*). The role of animal (saturated) fat as a risk factor for type 2 diabetes, as opposed to the protective role played by vegetable (unsaturated) fat, has been recently confirmed in a cross-sectional study on a European population (Thanopoulou *et al.* 2003) and is further supported by evidence from studies where dietary fat composition was assessed by objective markers of fat intake (Vessby *et al.* 1994; Laaksonen, 2002; Wang *et al.* 2003).

Few epidemiological studies have evaluated the effects of long-chain *n*-3 fatty acids on the risk of diabetes (Table 3). High concentrations of these fatty acids, mainly EPA and docosahexaenoic acid, are found in fish oil (Feskens & van Dam, 1999). In a study of 175 elderly subjects an inverse association was observed between fish intake and incidence of impaired glucose tolerance or diabetes, with an odds ratio 0·47 (95 % CI 0·23, 0·93) for participants consuming any type of fish (mean daily intake 24·2 g; Feskens *et al.* 1991). Consistent with this finding is the inverse association between increased fish consumption and incidence of type 2 diabetes observed in the Nurses' Health Study (Salmeròn *et al.* 2001), while in the Iowa Women's Study a higher *n*-3 intake was even associated with an increased risk of type 2 diabetes (Meyer *et al.* 2001).

In short, available epidemiological data suggest a potentially beneficial effect of vegetable (unsaturated) fat and a potentially adverse effect of animal (saturated) fat and

Table 2. Major prospective studies on dietary fat and risk of type 2 diabetes

Study	Subjects (*n*)	Diet assessment	Follow-up (years)	Relationship with dietary fat*		
				Total	Saturated (animal)	Unsaturated (vegetable)
Gothenburg (Lundgreen *et al.* 1989)	1462	24 h recall	12	No	n.a.	n.a.
St Luis Valley (Marshall *et al.* 1994)	134	24 h recall	1–3	↑	↑	↑
Zutphen Study (Feskens *et al.* 1995)	338	Diet history	30	↑	↑	No
Uppsala (Vessby *et al.* 1994)	1828	Cholesteryl ester fatty acids	10	n.a.	↑	↓
Nurses' Health Study (Salmeròn *et al.* 2001)	84 204	Food frequency	14	No	↑ (?)	↓
Iowa Women's Health Study (Meyer *et al.* 2001)	35 988	Food frequency	11	No	↑ (?)	↓
Health Professionals' Study (Van Dam *et al.* 2002)	42 504	Food frequency	12	↑	↑	No
Eastern Finland (Laasksonen *et al.* 2002)	895	Food record and serum fatty acids	4	No	No	↓
ARIC Study (Wang *et al.* 2003)	2909	Cholesteryl ester and phospholipid fatty acids	9	n.a.	↑	↓

n.a., not ascertained; ARIC, Atherosclerosis Risk in Communities.
* Independent of body-weight changes.

Table 3. Major prospective studies on long-chain *n*-3 fatty acids or fish intake and risk of type 2 diabetes

Study	Subjects (*n*)	Follow-up (years)	Category	Relative risk*	95 % CI
Zutphen Study (Feskens *et al.* 1991)	175	4	Fish-eaters	0·47	0·23, 0·93
Seven Countries Study (Feskens *et al.* 1995)	338	20	Increase in fish consumption	↓ 2 h blood glucose	
Iowa women (Meyer *et al.* 2001)	35 988	11	5th quintile *v.* 1st quintile *n*-3 intake	1·15	1·00, 1·33
Nurses' Health Study (Salmeròn *et al.* 2001)	84 204	14	5th quintile *v.* 1st quintile *n*-3 intake	0·80	0·67, 0·95

* Multivariate model including amount and type of fat.

trans fatty acids on the risk of type 2 diabetes (Hu & van Dam, 2001). Total fat intake does not seem to predict *per se* the development of type 2 diabetes, although when consumed in large amounts it may indirectly influence the development of this condition by facilitating the occurrence of overweight (Mayer-Davis *et al.* 1997; Marshall & Bessensen, 2002). There are, however, no controlled intervention trials evaluating the effects of different types of fat on the incidence of diabetes. One study evaluated the effects of a reduced-fat diet for 5 years in 176 individuals with impaired glucose tolerance. Glucose tolerance improved in patients on the reduced-fat diet, with a lower proportion of subjects developing type 2 diabetes at 1 year (47 *v.* 67 %, $P<0{\cdot}05$), although the differences between groups waned with time. However, since in the intervention group there was also a significant reduction of body weight (almost 3 kg) in the first 3 years, it is difficult to differentiate between the effect of fat intake *per se* and that mediated by weight loss on the risk of developing diabetes (Swinburn *et al.* 2001).

In summary, the available evidence (derived almost exclusively from observational studies) indicates that shifting from a diet predominantly based on fat from animal sources to a diet in which vegetable fat is more often employed might be beneficial in relation to the prevention of type 2 diabetes. An exception to this paradigm may be represented by fish consumption, since in some studies it is associated with a lower risk of diabetes. Whether the protective effect of fish is due to its *n*-3 fatty acid content (Adler *et al.* 1994) or to other components, such as protein, is matter of debate (Lavigne *et al.* 2001). In this respect, it is worth mentioning that the intake of foods rich in *n*-3 fatty acids other than fish is associated with a lower risk of type 2 diabetes (Jiang *et al.* 2002).

The mechanism by which dietary fat consumption could influence the development of diabetes is strictly linked with insulin sensitivity: dietary fat can influence insulin sensitivity independently of any change in body weight. Animal studies have clearly shown that a high-fat diet, particularly a diet high in saturated fat, decreases insulin sensitivity (Storlien *et al.* 1991). Several cross-sectional studies have examined dietary fat in relation to fasting and post-load plasma insulin concentrations, which are both markers of insulin resistance. The consistent finding is a positive association between saturated fat intake and hyperinsulinaemia, independently of body fat. These data have been partially confirmed in human studies using more accurate techniques to evaluate insulin resistance (Vessby, 2000). An association between dietary fat quality and insulin sensitivity is also supported by the significant relationship between insulin sensitivity and the fatty acid composition of body tissues, which is dependent on the fatty acid composition of the diet (Vessby *et al.* 1994). A problem with these studies, however, is that most fatty acids are closely interrelated and, therefore, insulin resistance or an increased risk of type 2 diabetes are characterised by a fatty acid 'pattern', rather than by the proportion of one or a few fatty acids.

The mechanisms linking dietary fat quality to insulin sensitivity are not completely understood; however, the effects of dietary fatty acids on insulin sensitivity are thought to be mediated, at least partially, through the fatty acid composition of cell membranes (Vessby *et al.* 1994; Storlien *et al.* 1996; Vessby, 2000). A specific fatty acid profile in cell membranes could influence insulin action through several potential mechanisms, including altered insulin receptor binding or affinity, and by influencing ion permeability and cell signalling. The results of human studies consistently show that the fatty acid composition of body tissues (serum lipids, phospholipid in erythrocyte membranes, triacylglycerol in adipose tissue, phospholipid in skeletal muscle membranes) reflects, at least in part, the fat composition of the habitual diet (Riccardi *et al.* 2004). The fatty acid pattern mirrors the average composition of the diet during the preceding weeks (serum lipids, erythrocytes), months (possibly skeletal muscle) and even years (adipose tissue). The strength of the relationships between the proportion of a specific fatty acid in the diet and in body tissues varies greatly between different fatty acids and for different tissues (Aro, 2003). Insulin resistance and insulin resistant states are associated with a plasma fatty acid pattern characterised by an increased proportion of palmitic acid and a low proportion of linoleic acid, with a distribution of other fatty acids that indicates an increased activity of Δ^9- and Δ^6-desaturase. These changes are probably related, to a large extent, to the type of fat in the diet and are consistent with a diet where animal (saturated) fat consumption is increased and vegetable (unsaturated) fat consumption reduced (Vessby *et al.* 2000)

More information on the issue of dietary fat quality and insulin sensitivity has emerged from the KANWU Study, which is the first intervention study on this topic, performed using adequate methodologies and a sufficiently large sample size (Vessby *et al.* 2001). This study involved 162 healthy individuals from five different countries, randomly assigned to consume diets high in saturated fat or monounsaturated fat without any change in other dietary

constituents; a randomly selected subsample within each group was also given fish-oil supplement or placebo. Insulin sensitivity (assessed by the frequent sampling intravenous tolerance test (minimal model)) was significantly impaired on the diet high in saturated fat (−10 %, $P=0{\cdot}05$) but remained unchanged on the diet high in monounsaturated fat. The *n*-3 fatty acid supplement did not influence insulin sensitivity in the whole study group, nor in those assigned to the diets high in saturated or monounsaturated fat.

The deteriorating effect of saturated fat on insulin sensitivity was supported by a subsequent controlled intervention study in which the comparison was performed between saturated fat and polyunsaturated fat (Summers *et al.* 2002); however, it was not confirmed in another study in which both the sample size and the study duration were inadequate (Lovejoy *et al.* 2002).

The KANWU Study (Vessby *et al.* 2001) did not attempt to modify total fat intake; however, if participants were stratified according to their habitual intake of total fat (above and below median value), the effect of fat quality on insulin sensitivity was clearly different between high- and low-fat groups. In the group consuming >37 % energy as total fat (median value of the study population), the difference between the effect of the high-saturated-fat and the high-monounsaturated-fat diet on insulin sensitivity almost completely disappeared; conversely, in those consuming <37 % energy as total fat, the difference between the two diets was even more striking (20·3 %, $P<0{\cdot}03$) (Fig. 1). This suggests that the total amount of fat can influence insulin sensitivity, and possibly the risk of type 2 diabetes, only when it exceeds a threshold level of 35–40 % total energy intake. This is in accordance with clinical studies showing that a moderate increase in total fat intake within current limits is unlikely to have a negative impact on insulin sensitivity (Parillo *et al.* 1992). In this regard, *n*-3 fatty acid supplementation does not seem to play a major role; this suggests that the relationship between fish consumption and risk of diabetes is complex, and that further studies are needed to clarify the possible underlying mechanisms and the existence of a dose–response relationship as well as gene–nutrients interactions.

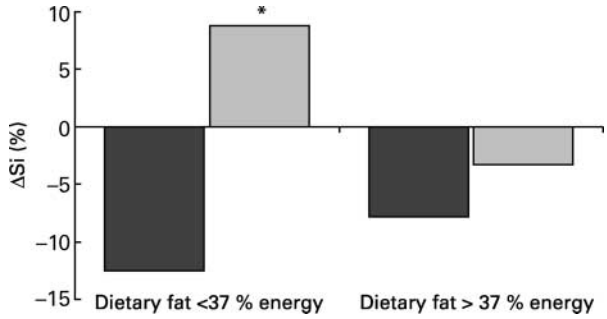

Fig. 1. Effect of a change of dietary fat quality on insulin sensitivity (S_i) when related to total dietary fat intake. Healthy subjects (*n* 162) were randomly assigned to consume either a high-saturated-fat or a high-monounsaturated-fat diet for 3 months. ■, High-saturated-fat diet; ▒, high-monounsaturated-fat diet. S_i sensitivity was assessed by frequent sampling intravenous glucose tolerance test (minimal model); participants were stratified on their habitual intake of total fat (above and below the median). Mean value was significantly different from that of the high-saturated-fat group: *$P<0{\cdot}03$. Reprinted with permission from the publishers of Vessby *et al.* (2001).

Alcohol

Several studies have evaluated the relationship between alcohol intake and diabetes; they are consistent in showing that moderate alcohol consumption (one to two drinks per d) is associated with a 30–40 % lower risk of type 2 diabetes compared with abstainers (Table 4) (Stampfer *et al.* 1988; Perry *et al.* 1995; Ajani *et al.* 2000; Conigrave *et al.* 2001; Carlsson *et al.* 2003; Nakanishi *et al.* 2003). In addition, various epidemiological studies have suggested that light to moderate alcohol consumption has beneficial effects on total mortality and morbidity (Stampfer *et al.* 1988; Keil *et al.* 1997; Muuntwyler *et al.* 1998; Conigrave *et al.* 2001).

Some studies, while confirming the beneficial effects of moderate alcohol consumption, highlight the possible dangers of high alcohol intake also in relation to diabetes prevention (Kao *et al.* 2001). In particular, they suggest a U-shaped relationship between alcohol intake and incidence of diabetes, with the risk being the lowest in light and moderate drinkers and the highest in heavy drinkers (Wei *et al.* 2000; Harding *et al.* 2002; Wannamethee *et al.* 2002, 2003; Nakanishi *et al.* 2003). Overall, these studies show that a moderate alcohol intake may have a protective effect on the risk of diabetes independently of the type of beverage. The beneficial effects of moderate intake of alcohol on diabetes incidence could be explained by the enhanced insulin sensitivity found in moderate alcohol drinkers (Facchini *et al.* 1994). However, benefits from moderate alcohol consumption on diabetes incidence could also be mediated by dietary exposures and other aspects of lifestyle associated

Table 4. Major prospective studies on moderate alcohol consumption and risk of type 2 diabetes

Study	Subjects (*n*)	Follow-up (years)	Moderate consumption *v.* none	
			Relative risk	95 % CI
Nurses' Health Study (Stampfer *et al.* 1988)	85 051	4	0·60	0·30, 0·90
British men (Perry *et al.* 1995)	7735	12·8	0·60	0·40, 1·00
Texas men (Wei *et al.* 2000)	8663	6	0·55	0·33, 1·00
US male physicians (Ajani *et al.* 2000)	20 951	12	0·57	0·43, 0·73
US Health Professionals' Study (Conigrave *et al.* 2001)	46 892	12	0·64	0·53, 0·77
Japanese men (Nakanisi *et al.* 2003)	2953	7	0·64	0·47, 0·93
Finnish Twin Cohort Study (Carlsson *et al.* 2003)	22 778	15	0·50	0·20, 1·50

with moderate drinking. The detrimental consequences of alcoholism on health and the dangers of combining alcohol and driving should be strongly emphasised when giving information on the possible beneficial effects of alcohol consumption on the risk of type 2 diabetes.

Intervention studies based on a multifactorial design

There are very few controlled intervention studies on lifestyle modifications and prevention of type 2 diabetes in the literature. In the Da Qing study (Pan *et al.* 1997) 577 patients with impaired glucose tolerance were randomly assigned to four groups (control, diet only, exercise only or diet plus exercise) and followed for 6 years. The incidence of diabetes decreased by 31 % in the diet group, by 46 % in the exercise group and by 42 % in diet plus exercise group, with no significant differences between the three. This beneficial effect was obtained with a minimal weight loss (about 0·5 kg) and increase in physical activity. This study is the first randomised controlled clinical trial showing that it is possible to reduce the risk of type 2 diabetes in individuals with impaired glucose tolerance by a lifestyle intervention; however, due to some methodological flaws, it was not received by the scientific community as conclusive evidence.

More recently, two studies have confirmed the importance of lifestyle modifications induced by a multifactorial intervention in the prevention of type 2 diabetes (Table 5): the Finnish Diabetes Prevention study and the Diabetes Prevention Program. These two studies had an appropriate study design and an up-to-date methodological approach, and their results therefore provide evidence that lifestyle modification represents a very effective and powerful way to decrease or delay the development of type 2 diabetes in overweight individuals at high risk.

In the Finnish study of Tuomìlehto *et al.* (2001), 522 overweight subjects with impaired glucose tolerance were randomly assigned to an active intervention group or a standard treatment group (general advice on diet and physical activity) and were followed for an average of 2–3 years. In the intervention group each subject received individual counselling aimed at achieving at least 5 % weight reduction, decreasing total and saturated fat intake, increasing fibre intake to at least 3·6 g/MJ and increasing physical activity to at least 30 min/d. After 2 years, the intervention group achieved a 3·5 kg weight loss and the control group 0·8 kg; the incidence of diabetes after 4 years was 11 (95 % CI 6, 15) % in the intervention group and 23 (95 % CI 17, 29) % in the control group, with a 58 % reduction in risk for diabetes in the intervention group. Given the multifactorial nature of the intervention, the study showed that diabetes prevention increased in parallel with the number of successful lifestyle changes achieved (body weight reduction <5 %, saturated fat <10 %, total fat <30 %, dietary fibre $>3{\cdot}6$ g/MJ, physical exercise of any type >4 h per week).

In the Diabetes Prevention Program Study (Diabetes Prevention Program Research Group, 2002) 3234 subjects with both impaired glucose tolerance and impaired fasting glucose were randomly assigned to three groups: control group; metformin group; lifestyle intervention group. In this last group the main aims were to reduce weight by 7 % and increase exercise to at least 150 min per week; diet composition was changed in the lifestyle intervention group, aiming at a reduced intake of fat, particularly saturated fat. In subjects assigned to the intensive lifestyle intervention, the incidence of type 2 diabetes was reduced by 58 % compared with the control group. Remarkably, this study shows that lifestyle intervention is significantly more effective than metformin, an antidiabetic drug, in diabetes prevention. In particular, this difference between lifestyle intervention and metformin was more pronounced in individuals aged >60 years and with a BMI <35 kg/m^2, who represent the large majority of the population at risk. The results of this study are in agreement with those of the Finnish study (Tuomìlehto *et al.* 2001), as both indicate that to prevent one case of diabetes, seven subjects with impaired glucose tolerance must be treated for 3 years.

These studies demonstrate that type 2 diabetes can be prevented by lifestyle changes. The interventions always included body-weight reduction, but involved multifactorial approaches that also considered changes in diet composition. The average amount of weight loss achieved in the lifestyle intervention groups was not large (about 5 % initial weight) and in any case was much less than the weight loss traditionally considered as clinically significant. Despite the common scepticism towards the capacity to induce lifestyle changes in overweight sedentary people, the two studies report a drop-out rate of only 9 % in the intervention group (not much greater than the 7 % observed in the control group); moreover, a large proportion of them

Table 5. Major controlled intervention studies on prevention of type 2 diabetes by lifestyle modifications

Study	Subjects (*n*)	Follow-up (years)	Intervention goals	Risk reduction (%)
Diabetes Prevention Study (Finland) (Tuomìlehto *et al.* 2001)	523	3·2	Weight reduction >5 % Total fat <30 % Saturated <10 % Fibre 3·6 g/MJ Exercise 30 min/d	58
Diabetes Prevention Program (USA) (Diabetes Prevention Program Research Group, 2002)	3234	2.8	Weight reduction >7 % Low-fat diet Exercise 150 min/week	58

were able to modify their lifestyles. However, we do not know whether the intervention programme was successful in influencing diet and physical activity in a sustained way. This is not a trivial problem since 3 or 4 years are only a small portion of an individual's life.

Noteworthy within this context is the importance of exercise in the prevention of diabetes, as demonstrated by these intervention studies: in the Da Qing Study the exercise group reported a 46 % decrease in incidence of type 2 diabetes (Pan *et al.* 1997); in the Finnish Diabetes Prevention Study, the intervention group who achieved the exercise goal (moderate exercise for at least 30 min/d) had an odds ratio 0·3 for diabetes compared with the control group (95 % CI 0·1, 0·7) (Tuomìlehto *et al.* 2001). Similar results were obtained in the Diabetes Prevention Program Study (Diabetes Prevention Program Research Group, 2002).

The beneficial effect of exercise on the risk of diabetes may act through a direct effect on insulin sensitivity or a decrease in body weight. There is considerable evidence that physical activity *per se* improves insulin resistance in normal subjects and diabetic patients (Ebeling *et al.* 1993; Dela *et al.* 1994; Mayer-Davis *et al.* 1998). In addition, in some cases it may also help to lose and maintain weight (if energy intake is kept under control).

Proposals for an integrated approach to reducing the risk of type 2 diabetes at the population level

For many years, those who are overweight and have sedentary lifestyles have been considered at risk for type 2 diabetes. However, until very recently no properly controlled studies were available to show that lifestyle changes can delay the onset of diabetes; therefore, any attempt to devote time and resources to set up a programme of primary prevention for type 2 diabetes was deemed inappropriate, not only at the political level, but also by the healthcare providers who deal with the devastating effects of this disease every day. In view of all the new evidence accumulated in the last 5–10 years, most of which has been reviewed in the present paper, the time has come to set up such a programme. However, whether primary prevention of type 2 diabetes is feasible and effective at the population levels still remains to be evaluated.

In many ways, this condition provides an ideal target for prevention, since it meets all the requirements that a primary prevention programme should have to be of real value: (1) high prevalence; (2) a serious condition with potentially disabling complications; (3) risk factors associated with lifestyle and that can be modified; (4) the possibility of identification of individuals at risk by screening (American Diabetes Association & National Institute of Diabetes, Digestive & Kidney Diseases, 2002).

Moreover, current evidence shows that lifestyle changes, to be effective, should not be 'heroic' so as to be sustainable for years (i.e. weight reduction of 4 kg or approximately 5 % initial weight) (Tuomìlehto *et al.* 2001; Diabetes Prevention Program Research Group, 2002). Some recent intervention studies clearly show that people from different countries, with different ethnic and socio-economic backgrounds, can modify their long-term dietary habits and level of physical activity if adequately motivated and supported. However, since the participants in these studies were at high risk for diabetes, the intervention employed was very intensive and consequently very demanding in terms of both economic resources and operators' time. It remains to be elucidated whether a less intensive intervention might be effective in modifying lifestyle and beneficially influencing diabetes prevention in the general population. The best approach would probably be a combination of a population strategy associated with a more intensive intervention targeted at high-risk individuals (American Diabetes Association and National Institute of Diabetes, Digestive and Kidney Diseases, 2002).

On the basis of the available evidence, it seems reasonable to attempt a multifactorial rather than a monofactorial intervention, because it allows more flexibility and thus accounts for the individual's capacity to act on and modify one or more lifestyle behaviours at risk (Hu *et al.* 2001; Perry, 2002; van Dam *et al.* 2002*b*). Moreover, since lifestyle modifications have an additive effect on diabetes prevention, a multifactorial approach might also amplify the efficacy of the intervention. Additional research is needed to identify the most cost-effective strategies for a sustained achievement. For the time being, however, patients with abnormalities of blood glucose regulation considered as being in a pre-diabetic state (impaired glucose tolerance or impaired fasting glucose) should undergo routine follow-up and be constantly advised to lose weight and increase their levels of physical activity to reduce the risk of type 2 diabetes. The lifestyle factors that have been consistently associated with increased risk of type 2 diabetes are overweight and physical inactivity. However, recent evidence from epidemiological studies reviewed in the present paper has shown that the risk of type 2 diabetes is also associated with: (1) a low fibre intake; (2) a high *trans* fatty acid intake and a low unsaturated fat:saturated fat intake ratio; (3) absence of or excess alcohol consumption. All these factors are extremely common in Western populations and therefore the potential impact of any intervention on them is large. Indeed, taking into account these risk factors for type 2 diabetes, only 9·5 % of women recruited in an observational study in the USA were in the low-risk category. The ability to correct these behaviours in the rest of the population was estimated to reduce the incidence of diabetes by as much as 87 % (Hu *et al.* 2001). However, incontrovertible evidence that each of these lifestyle modifications can reduce the risk of diabetes is not available, since controlled intervention studies with a monofactorial design have not been produced for these measures.

In conclusion, it is possible to achieve primary prevention of type 2 diabetes by means of intensive interventions in high-risk individuals, in whom they have proven to be effective. Appropriate strategies to identify high-risk individuals in a simple and inexpensive way are urgently warranted. Although the benefits of a less intensive intervention at the level of the general population cannot be presently quantified, it seems reasonable to convey appropriate messages to the public in order to modify the extremely common habits associated with an increased risk of type 2 diabetes. This is especially desirable since they are also linked with an high risk for CVD. New

emphasis on prevention might limit the dramatic worldwide increase in the incidence of type 2 diabetes expected in next few years.

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